A STUDY OF A NEUROPSYCHOLOGICAL ASSESSMENT OF HIV PATIENTS ON ART

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TIRUNELVELI

CERTIFICATE

This is to certify that this dissertation entitled " **A study of a Neuropsychological assessment of HIV patients on ART"** submitted by **Dr. K.Shunmuga Sundaram** appearing for D.M., Degree examination in August 2012 is a bonafide record of work done by him under my direct guidance and supervision in partial fulfillment of regulations of the Tamil Nadu Dr.M.G.R. Medical University, Chennai. I forward this to the The Tamil Nadu Dr.M.G.R. Medical University, Chennai.

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This is to certify that the Institutional Ethical Committee of this College unanimously approves the Thesis /Dissertation/ Research Proposal submitted before this committee by Dr. K.SHUNMUGA SUNDARAM a **SUPERSPEICALITY** in the Department of **NEUROLOGY**, of Tirunelveli Medical College /Hospital, Tirunelveli titled **"A STUDY OF NEURO PSYCHOLOGICAL ASSESSMENT IN HIV PATIENTS ON ART"** registered by the IEC as 056/Neuro./IEC/2011 dated: 25.02.2011. The Investigator is hereby advised to adhere to all the stipulated norms and conditions of this ethical committee.

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DECLARATION

I Dr.K. Shunmuga Sundaram do solemnly affirm that this dissertation titled " **A study of a Neuropsychological assessment of HIV patients on ART"** is done by me at Department of Neurology, Tirunelveli Medical College & Hospital, Tirunelveli, during the year 2011 - 2012 under the guidance and supervision of Dr.S.Saravanan, M.D., D.M., Professor and Head, Department of Neurology, Tirunelveli Medical college. The dissertation is submitted to The Tamilnadu Dr.M.G.R.Medical University towards the partial fulfillment of requirements for the award of D.M., degree in Neurology.

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Introduction

INTRODUCTION

HIV infection is one of the most common health problems in modern world. Neuropsychological impairments are well described in patients with HIV infection from very early days. Prior to the antiretroviral therapy, HIV infection causing AIDS leading to dementia was high and the cumulative risk of developing HIV associated dementia was estimated between 15 – 20% in 1993. In the era of highly active anti retroviral therapy (HAART), the clinical spectrum of neuropsychological impairment changed from severe HIV associated dementia in advanced AIDS to more minor forms of neuropsychological impairment which can be managed with adequate therapy with ART and other supportive therapies.

Early identification of asymptomatic neuropsychologically impaired patients by means of neurologic examination and neuropsychological assessment will be useful in the prevention and (or) reduction of neuropsychological impairment in their every day functioning of life.

The neuropsychological decline in HIV patients occur in all stages of infections and it may be modified by factors like ART. So there is a growing need to find out prevalence of neuropsychological impairment and types of neuropsychological impairment in patients with HIV infection and to find out factors that will influence the occurance of neuropsychological

impairment. Modification of factors that will influence neuropsychological impairment may help to improve the outcome of neuropsychological impairment in this HIV infected patients on ART.

Aim of the study

AIMS OF THE STUDY

1. To assess the prevalence of neuropsychological impairment among HIV positive patients on AntiRetroviral Therapy(ART).

2. To study the pattern of neuropsychological impairment in the study population.

3. To study the factors that may influence the occurance of neuropsychological impairment in HIV positive patients on ART .

Review of literature

REVIEW OF LITERATURE

HIV is a globally present most common sexually transmitted disease in humans. Infection with Human Immuno deficiency Virus type 1 (HIV-1) cause severe damage to immune system thereby causing severe immuno deficiency state leading to increased chances of acquiring opportunistic infections and malignancies. HIV infection affects almost all systems of the body.

HIV is a neurotropic virus that invades the brain directly shortly after infection. HIV replicates in macrophages and microglia, thereby causing inflammatory and neurotoxic host responses. Persistent infection and inflammation of nervous system by HIV-1 infection leads to chronic HIV-1 infection causing dysfunction in both central nervous system and peripheral nervous systems. Chronic HIV-1 infection can result in neurodegenerative disease causing cognitive, behavioural and motor difficulties.

The neuropsychological impairments caused by HIV-1 infection includes decreased attention/concentration, psychomotor speed, memory, learning, information processing and executive function. There is also motor slowing, incoordination, and tremor, that may progress to disabling weakness, spasticity, extrapyramidal movement disorders and paraparesis.

Epidemiology of HIV infection:

According to **UNAIDS 2011** report, at the end of 2010, an estimated 34 million people were living with HIV globally, including 3.4million children less than 15 years. There was 2.7 million new HIV infection in 2010, including 3,90,000 among children less than 15 years.

Globally, the annual number of people newly infected with HIV continues to decline, although there is stark regional variation. In sub Saharan Africa, where most of the people newly infected with HIV live, an estimated 1.9 million people become infected in 2010. This was 16% fewer than the estimated 2.2 million people newly infected with HIV in 2001.

The annual number of people dying from AIDS related causes worldwide is steadily decreasing from a peak of 2.2 million in 2005 to an estimated 1.8million in 2010. The number of people dying from AIDS related causes began to decline in 2005-2006 in sub-Saharan Africa, South and South East Asia and the Caribbean and has continued subsequently.

HIV epidemic in India is concentrated in nature. The HIV prevalence among the High Risk Groups ie, female sex workers, injecting drug users, men who have sex with men and transgenders is about 20 times higher than the general population.(**NACO ANNUAL REPORT-2011**). Analysis of epidemic projections revealed that the number of new annual HIV infections had declined by more than 50 percent during the last decade, 2.7 lakh in 2000 to 1.2 lakh in 2009.

The estimated adult HIV prevalence in India was 0.32% (0.26% - 0.41%) in 2008 and 0.31% (0.25 – 0.39%) in 2009. The adult

prevalence is 0.25 percent among women and 0.36 percent among men in 2009.

The total number of people living with HIV / AIDS (PLHA) in India is estimated at 23.9 lakh (19.3 – 30.4 lakh) in 2009.

Children under 15 years account for 3.5 percent of all infections, while 83 percent are in age group 15 – 49 years. Of all HIV infections, 39 percent (9.3 lakh) are among women. The four high prevalence states of South India (Andra Pradesh -5 lakh; Maharastra 4.2 lakh) Karnataka -2.5 lakhs, Tamilnadu -1.5 lakh) account for 55 percent of all HIV infections in the country.

In Tamilnadu, there are 40 ART centers. Total number of adult PLHA receiving ART is 45,179 and total number of pediatric PLHA receiving ART is 2,776. Totally 47,955 patients are getting ART in Tamilnadu as on Dec 2010.

In India adults 3,61,889 patients and pediatric patients 22,837 are on ART as on Dec 2010.

CD4 cell count and ART:

In Tirunelveli Medical College Hospital, ART Centre was started in the year 2005. Till the end of 2011, totally 5515 patients were registered in the ART centre of which 2325 patients were enrolled for ART treatment. During this more than 6 years of ART service, 1099 patients died. Initially ART was started when CD4 count falls below 200 cells / mm^3. From 13th April 2009, it was revised to 250 cells /mm^3. From November 2011 onwards, NACO advised to issue ART, when CD4 count is less than 350 cells/ mm^3.

So more number of patients with HIV will receive ART and HIV infection related morbidity and mortality can be reduced.

Global epidemiology of HIV and (HAND) HIV associated, Neuropsychological disorders:

HIV is an important global disease, especially affecting sexually active, working populations of the society. HIV is affecting approximately 34 million people all over the world. Most of the people infected (or) affected by HIV live in developing countries. Africa and the Middle East countries account for over two thirds (>66%) of world wide HIV infections, Asia for over 20%, Eastern Europe and Central Asia for approximately 4% and Latin America and the Caribbean for around 6% (**Hemelaar et al 2006**).

The rapid evolution of the virus itself has led to considerable genetic variation in a relatively short period. In West Central Africa, almost all of the nine major subtypes of HIV-1 group M (A-D, F-H, J and K) as well as strains of HIV-1 groups N and O, and HIV-2 can be found. In other parts of Africa and other regions of the world however, certain subtypes and recombinant forms such as CRF 01_AE and CRF 02_AG predominate over others (**Hemelaar et al 2006**).

Neuropathology:

HIV-1 enters the CNS early during the course of infection (**An et al 1999; Davis et al 1992**) and causing significant loss of nervous and neuronal processes and frequently results in neurological disorders with cognitive, motor and behavioral symptoms. The significant loss of nervous and neuronal processes (eg. Dendritic complexity) in people dying of AIDS clearly correlates with ante-mortem neuropsychological impairment (**Masliah et al 1992; Mattson et al 2005**).

Cells primarily infected by HIV in CNS are blood derived macrophages, resident microglia, and astrocytes, but most studies suggest that neurons are not directly infected (**Epstein and Gendelman 1993; Trillo-Pazo et al 2003**).

The Neuronal damage occurs in HIV infection is due to shed viral proteins such as gp 120 (**Dreyer et al 1990**) and Tat (**Jones et al 1998; Natts et al 1999; Betmisch et al 2004**) (or) indirectly through neurotoxic molecules released by activated astrocytes (**Nath et al 1999**) macrophages and microglia. (**Mattson et al 2005; Hammerle et al 2005**).

HIV infection in the brain has widespread and also variable effects. It appears to preferentially cause damage to the basal ganglia and deep white matter (**Navia et al 1986a**). However, HIV infection causing damage to cortical and sub cortical neurons (hippocampus and putamen), particularly with dendritic pathology can also likely to play a role in CNS disease manifestations.

Nomenclature:

Navia et al initially recommended the term AIDS Dementia Complex to label the severe neuropsychological loss and neurological dysfunction associated with advanced immunodeficiency (**Navia et al 1986b**). Then, the American Academy of Neurology suggested HIV Associated Dementia as a better label (**AAN 1991**). Patients with some degree of cognitive impairment but whom did not meet criteria for dementia were classified as having Minor cognitive motor disorder in the AAN nomenclature.

With true HIV Associated Dementia, patient profile were marked by severe behavioral changes, attention and executive dysfunction, psychomotor slowing and memory impairment (**Bornstein et al 1993; Stem et al 2001**). Minor cognitive motor disorder patient profiles were characterized by impaired cognitive and motor speed, working memory and new learning, but many aspects of language (except fluency) and long term (semantic) memory were relatively unimpaired.

For research and epidemiological purposes HIV Associated Neuropsychological Disorders (HAND) be used as a more comprehensive titles with three broad subdivisions depending on the degree of cognitive impairment and its impact on every day functioning.

a) Asymptomatic Neuro cognitive Impairment (ANI)

ANI is defined by decline in performance by at least 1 standard deviation (SD) below the mean of demographically adjusted normative scores in at least two cognitive areas (Attention-working memory, speed of information processing, language, abstraction – executive function, complex motor skills, memory including learning and recall, simple motor skills, (or) sensory perceptual abilities), but without any apparent changes in activities of daily living.

b) Mild Neuropsychological Disorder (MND)

It is previously referred as minor cognitive and motor disorder, features the same test performance criteria as above, but with notable changes (at least mild) in activities of daily living.

c) HIV Associated Dementia (HAD)

It requires decline in performance by atleast 2 SD below demographically corrected normative means in at least two different cognitive areas, as well as marked difficulty in activities of daily living due to cognitive impairment (Antinori et al 2007).

Diagnosis of all three forms of HAND also requires a determination that the observed neuropsychological impairment and / or functional disturbance cannot be explained by co-morbid (non HIV related) conditions.

Now the severe forms of HAND are far less common, this classification system has been geared more towards mild and even asymptomatic impairment. As a consequence the new

system may give better estimates of neuropsychological disorders than AIDS Dementia Complex.

This updated classification system, based on both neuropsychological test performance and its effects on day to day activities (including activities of daily living and functional abilities).

Patterns of Neuropsychological Dysfunction:

Human Immuno deficiency Virus infection characteristically produces a "sub-cortical" pattern of neuropsychological dysfunction with deficits predominantly seen in executive functions, attention and working memory, motor speed, speed of information processing, new learning and retrieval of new information, while long term (semantic) memory, many language skills, and visuo-spatial abilities may remain intact (Dawes et al 2008; Grount et al 1987; Heaton et al 1995).

This average pattern of neuropsychological impairment reported by numerous studies before and after the advent of highly active anti retroviral therapy, has helped in the development of various test batteries which are also presently used in the assessment of neuropsychological functions in HIV patients.

It is rare to have HIV infected people without comorbidities in most parts of the world. Excluding comorbidities, especially in resource limited countries like sub-Saharan Africa, makes the sample less representative of the broader HIV-infected populations, but it gives more confidence that any impairment

discovered on examination is directly due to HIV. Also, the prevalence and impact of various comorbid clinical conditions may vary across various international countries.

HIV Associated Neuropsychological Disorders in Developed and Developing countries:

Prior to era of highly active anti retroviral therapy, the cumulative risk of developing HIV associated dementia was about 15 – 20% (**Mc Arthur et al 1993**). Incidence of HIV dementia in the MACS cohort was estimated to decrease by 53% from 21.1 per 1000 person years between 1990 to 1992, to 10.5 per 1000 persons years between 1996 to 1998 (**Sacktor et al 2001**).

The clinical spectrum of the disease has shifted from the severe and devastating form of dementia commonly seen in association with advanced AIDS (end stage disease) before the introduction of protease inhibitors and highly active anti retroviral therapy (HAART) , to the milder and more manageable forms of HAND.

More recent studies conducted in patients on HAART, estimate that the prevalence of neuro cognitive dysfunction (based on neuropsychological assessments) in HIV populations ranges from 20 – 37% even with treatment (**Robertson et al 2007b; Sacktor et al 2001;**). The CHARTER study group recently presented findings from comprehensive neuropsychological evaluations lasting from 2 to 2.5 hours on a large unselected population of 1,555 HIV positive patients and reported that,

overall, 45% of cohort had neuropsychological impairment, based on a global neuro psychological rating (Heaton et al 2009).

The most remarkable outcome following the introduction of protease inhibitor (PI) and combination therapy was the dramatic decrease in CNS opportunistic diseases such as cryptococcal meningitis, cerebral toxoplasmosis, primary CNS lymphoma and progressive multifocal leukoencephalopathy (**d'Arminio Monforte et al 2004**). In poor countries these opportunitic CNS diseases and CNS infections by Mycobacterium tuberculosis, plasmodium species and other pathogens remain common.

The prevalence of HIV-Associated Dementia in sub-Saharan Africa has been reported to be from as low as 3% to as high as 54%. (**Howlett et al 1989**) at least in a part due to differences in definition and methods used.

Clifford et al (2007) report that International HIV Dementia Scale, a brief screening tool, did not detect any significant differences in cognitive status between HIV positive and negative subjects in Ethiopia consistent with clinical impression (**Clifford et al 2007**). Contrastingly, studies in India, China and Uganda reported prevalence rates of 56%, 34%, and 31% respectively (**Heaton et al 2008; Robertson et al 2007a ; Yepthomi et al 2006**). HIV-1 sub type C predominates in India, subtype B and CRF 01-AE in China, and sub types A and D in Uganda.

In a larger study of former plasma donors in rural China, Heaton et al (2008) administered the international test battery to 203 HIV positives and 198 HIV negative adults, mostly farmers (mean education = 5 – 6 years) (Heaton et al 2008) and results

showed 37% of HIV positive group as impaired based on neuropsychological assessments.

Another study which evaluated the pattern of neuropsychological performance in a sample of HIV positive patients and HIV negative control subjects in Uganda showed significant group differences on measures of verbal learning and memory, speed of information processing, attention and executive functioning (**Robertson et al 2007a**).

Gupta et al. (2007) compared a sample of 119 adults in India infected with HIV-1 sub type C who were not on antiretroviral therapy, with normative data derived from an Indian sample of 540 healthy volunteers (with comparable gender distribution, age, and education) and with a matched cohort of 126 healthy, HIV-1 – seronegative individuals (**Gupta et al.2007**). They found a high rate (60.5%) of mild to moderate cognitive deficits in the HIV patients but no evidence of true dementia. The neuropsychological profile was characterized by deficits in fluency, working memory, and learning and memory, once again similar to patterns that have been observed in the West.

A study reporting HIV-1 subtype-associated differences in neurological disease was recently reported by **Sacktor et al (2007**).

In the first randomized clinical trial observing neuropsychological effects of antiretroviral treatment in treatment naïve patients from multiple resources limited settings, Robertson et al. (2009) found substantial improvement across multiple time points of follow up from week 24 out to week 96 across seven resource limited setting countries (**Robertson et al. 2009**). The

analysis was limited to 293 participants who were randomized to treatment with didanosine enteric-coated (ddI) + emtricitabine (FTC) + atazanavir (ATV) in the AIDS Clinical Trials Group (ACTG) Study A5175 (PEARLS) , and did not include groups on alternate treatment regimens or untreated control groups for comparison.

Significant improvements in neuropsychological functioning after initiating antiretroviral therapy were determined after controlling for baseline function, age, sex, country, CD4, plasma HIV-1 RNA strain, and years of education. Notably, the magnitude of improvement in neuropsychological functioning varied across the countries and could not be explained by systemic disease factors. Improved neuropsychological functioning may be due to control of HIV viral load through antiretroviral therapy effects, uncontrolled practice effects on repeated test administrations or both.

STAGING

HIV disease staging and classification systems are critical tools for tracking and monitoring the HIV epidemic and clinical management. Two major classification systems currently are in use: the U.S. Centers for Disease Control and Prevention (CDC) classification system and the World Health Organization (WHO) Clinical Staging and Disease Classification System.

The CDC disease staging system assesses the severity of HIV disease by CD4 cell counts and by the presence of specific HIV-related conditions. The definition of AIDS includes all HIV-

infected individuals with CD4 counts of <200 cells/μL (or CD4 percentage <14%) as well as those with certain HIV-related conditions and symptoms. The CDC system is used in clinical and epidemiologic research.

In contrast to the CDC system, the WHO Clinical Staging and Disease Classification System (revised in 2005) can be used readily in resource-constrained settings without access to CD4 cell count measurements or other diagnostic and laboratory testing methods. The WHO system classifies HIV disease on the basis of clinical manifestations that can be recognized and treated by clinicians in diverse settings, including resource-constrained settings, and by clinicians with varying levels of HIV expertise and training.

CDC Classifications System for HIV Infection

The CDC categorization of HIV/AIDS is based on the lowest documented CD4 cell count (Table 1) and on previously diagnosed HIV-related conditions (Tables 2 and 3). For example, if a patient had a condition that once met the criteria for Category B but now is asymptomatic, the patient would remain in Category B. Additionally, categorization is based on specific conditions, as indicated below. Patients in categories A3, B3, and C1-C3 are considered to have AIDS.

Table 1. CDC Classification System for HIV-Infected Adults and Adolescents.

	Clinical Categories		
CD4 Cell Categories	A Asymptomatic, Acute HIV, or PGL (Persistant generalized lymphadenopathy)	B Symptomatic Conditions, not A or C	C AIDS-Indicator Conditions
(1) ≥500cells/μL	A1	B1	C1
(2)200-499 cells/μL	A2	B2	C2
(3) <200 cells/μL	A3	B3	C3

Table 2. CDC Classification System : Category B Symptomatic Conditions

Category B symptomatic conditions are defined as symptomatic conditions occurring in an HIV-infected adolescent or adult those meet at least 1 of the following criteria:

a) They are attributed to HIV infection or indicate a defect in cell-mediated immunity.
b) They are considered to have a clinical course or management that is complicated by HIV infection.

Examples include, but are not limited to, the following:

- Bacillary angiomatosis
- Oropharyngeal candidiasis (thrush)
- Vulvovaginal candidiasis, persistent or resistant
- Pelvic inflammatory disease (PID)
- Cervical dysplasia (moderate or severe) / cervical carcinoma situ
- Hairy leukoplakia, oral
- Idiopathic thrombocytopenic purpura
- Constitutional symptoms, such as fever (>38.5^{0}C) or diarrhea lasting >1 month
- Peripheral neuropathy
- Herpes zoster (Shingles), involving ≥2 episodes or ≥1 dermatome

Table 3. CDC Classification System : Category C AIDS-Indicator Conditions

- Bacterial pneumonia, recurrent (≥ 2 episodes in 12 months)
- Candidiasis of the bronchi. Trachea, or lungs
- Candidiasis, esophageal
- Cervical carcinoma, invasive, confirmed by biopsy
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1-month duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Encephalopathy, HIV-related
- Herpes simplex : Chronic ulcers (>1-month duration), or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1-month duration)
- Kaposi sarcoma
- Lymphoma, Burkitt, immunoblastic, or primary central nervous system
- Mycobacterium avium complex (MAC) or M kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis, pulmonary or extrapulmonary
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis jiroveci (formerly carinii) pneumonia (PCP)
- Progressive multifocal leukoencephalopathy (PML)
- Salmonella septicemia, recurrent (nontyphoid)
- Toxoplasmosis of brain
- Wasting syndrome due to HIV (involuntary weight loss >10% of baseline body weight) associated with either chronic diarrhea (≥2 loose stools per day ≥1 month) or chronic weakness and documented fever ≥1 month

WHO Clinical Staging of HIV / AIDS and Case Definition

. The clinical staging and case definition of HIV for resource-constrained settings were developed by the WHO in 1990 and revised in 2007. For the purpose of the WHO staging system, adolescents and adults are defined as individuals aged ≥15 years.

Clinical Stage I:

. Asymptomatic

. Persistent generalized lymphadenopathy

Clinical Stage II:

- Moderate unexplained * weight loss (under 10% of presumed or measured body weight)**
- Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis)
- Herpes zoster
- Angular chelitis
- Recurrent oral ulceration
- Papular pruritic eruptions
- Seborrhoeic dermatitis
- Fungal nail infections

Clinical Stage III:

- Unexplained* severe weight loss (over 10% of presumed or measured body weight)*
- Unexplained* chronic diarrhea for longer than one month
- Unexplained* persistent fever (intermittent or constant for longer that one month)
- Persistent oral candidiasis

- Oral hairy leukoplakia
- Pulmonary tuberculosis
- Severe bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
- Unexplained* anaemia (below 8g/dl), neutropenia (below 0.5 billion/l) and / or chronic thrombocytopenia (below 50 billion/l)

Clinical stage IV:

- HIV wasting syndrome
- Pneumocystis pneumonia
- Recurrent severe bacterial pneumonia
- Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site)
- Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
- Extrapulmonary tuberculosis
- Kaposi sarcoma
- Cytomegalovirus infection (retinitis or infection of other organs)
- Central nervous system toxoplasmosis
- HIV encephalopathy
- Extrapulmonary cryptococcosis including meningitis
- Disseminated non-tuberculous mycobacteria infection
- Progressive multifocal leukoencephalopathy
- Chronic cryptosporidiosis
- Chronic isosporiasis
- Disseminated mycosis (extrapulmonary histoplasmosis, coccidiomycosis)

- Recurrent septicaemia (including non-typhoidal Salmonella)
- Lymphoma (cerebral or B cell non-Hodgkin)
- Invasive cervical carcinoma
- Atypical disseminated leishmaniasis
- Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

Footnotes:

- *Unexplained refers to where the condition is not explained by other conditions.
- ** Assessment of body weight among pregnant woman needs to consider the expected weight gain of pregnancy.

Anti retroviral therapy:

In the initial years, HIV infection and AIDS was treated with Zidovudine. After the discovery of protease inhibitors, combination therapy against HIV infection initiated with One Nucleoside Reverse Transcriptase Inhibitor, One Non-Nucleoside Reverse Transcriptase Inhibitor. This various combination of antiretroviral drugs regimen is called as Highly Active Anti Retroviral Therapy (HAART).

A neurologically active anti retroviral drugs are; Nevirapine, Efavirenz, Stavudine, Zidovudine, Lamivudine, Abacavir and Indinacir. Principles for selecting the first line regimen in HIV infection (NACO guideline)

i) Choose one NRTI - Stavudine (or) Zidovudine

ii) Choose one NNRTI (Nevirapine (or) Efavirenz)

iii) Choose Lamivudine in all regimens.

In our ART centre in Tirunelveli Medical College Hospital, commonly used first line ART regimen are

- SLN - Stavudine, Lamivudine and Nevirapine
- ZLN – Zidovudine, Lamivudine and Nevirapine
- SLE – Stavudine, Lamivudine and Efavirenz
- ZLE – Zidovudine, Lamivudine and Efavirez

If CD4 count is not increasing with first line regimen (or) decreasing from previous level, then plasma viral load estimation with be carried out and second line regimen will be started.

Zidovudine:

Zidovudine was the first anti retroviral drug approved for the treatment of HIV infection and belongs to the group of drug called Nucleoside Reverse Transaiptase Inhibitors (NRTIs). The currently recommended dose of AZT is 300 – 600mg per day. Main side effects seen with AZT are anemia, leucopenia, ulcers in lips, mouth and tongue, bone marrow depression, loss of appetite, myalgias, bleeding tendency.

Stavudine (d4T):

Stavudine belongs to the group of drug NRTI. Commonly used as 100mg daily, in adults more than 60kg weight. Common side effects noted are peripheral neuropathy, pancreatitis and lipoatrophy.

Lamivudine:

One of the commonly used (3TC) NRTI group drug in ART. Dose used is 150mg twice daily (or) 300mg once daily. Side effects are rare when compared to Zidovudine and Stavudine.

Nevirapine (NVP):

Belongs to the group of drug called Non Nucleoside Reverse Transcriptase Inhibitors (NNRTI). Started with 200mg daily for 2 weeks followed by 400mg once daily. Side effects noted are skin rash, hepatitis and severe life threatening hepato toxicity observed when used with initial CD4 count >250 cells / mm^3 in women and >400 cells / mm^3 in men.

Efavirenz (EFV):

Another drug of NNRTI group commonly used in ART. Dosage is 600mg once daily. Efavirenz to be taken on empty stomach and avoid taking after high fat meals because of inceased peak concentration. Side effects noted are dizziness, somnolence, insomnia, abnormal dreams and teratogenicity.

After the introduction of HAART in HIV infection, various studies analyzed the effectiveness of HAART in the Neuropsychological impairment in HIV patients in all over the world.

Sacktor et al in 1998 studied the effect of HAART in the neuropsychological impairment due to HIV infection. Study group comprised of 474 homosexuals and followed for two years from 1995 to 1997 after administration of HAART. Results revealed that HAART participants showed better performance over the one year period of treatment in psychomotor speed and speed of information processing in Trail making Test B, when compared to antiretroviral naïve patients.

Tozzi et al in 2004 studied 70 patients on HAART and study results revealed that neuropsychological impairment in patients receiving HAART was associated with reduced Health Related Quality of life (HRQOL).

Lucette et al in (2004) did a study on 97 HIV positive patients and 41 patients were studied on Neuro active HAART with better Blood Brain Barrier (BBB) penetration and 56 patients with HAART. The results showed that both groups did not differ from one another on neuropsychological performance and the neuro HAART group showed significantly better memory performance its on the HAART group.

Neuropsychological assessment in HIV infected populations:

In 1989, National Institute of Mental Health NIMH conducted workshop on "Neuropsychological Assessment Approaches", neuropsychological test batteries should directly assess the areas of function that are deficient. Test batteries measures processes in the following seven cognitive domains, attention, verbal and visual memory, information processing speed, abstraction and executive functioning, language, visuospatial, and visuo constructive and motor.

While the existing literature reveals several various test measures are commonly used and widely accepted in the assessment of neuropsychological impairment due to HIV-1 infection, there is not a single specific battery (or) empirically validated "gold standard". Traditional batteries such a certain

measures from Halstead – Reitan Battery, measures assessing memory, and the Wechsler Adult Intelligence Scales appear to be the most frequently used (**Gonzalez et al 2003**). The aforementioned 1989 NIMH workshop continues to be the guiding force in determining which measures to use to assess HIV related cognitive decline. (**Carey et al 2004; Gonzalez et al 2003**).

For the assessment of premorbid intelligence WAIS-R vocabulary, National Adult Reading Test and Raven's Standard progressive matrices are used.

For testing the attention / working memory domain, WAIS-R, Digit spasm, Digit Vigilance, Paced Auditory Serial Addition Test (PASAT), Trail Making Test-A, Antisaccadics Eye movements for 20 commands etc are used.

For assessing the domain of learning and memory, California verbal learning Test (CVLT), Reproduction Test (WMS), Story learning, story memory delay free recall, figure learning, figure memory delay free recall, recall of 4 words, etc are used in various batteries.

For assessing the speed of processing, commonly available test batteries include WAIS-Digit symbol substitution test, Digit vigilance, Trail making test A, WAIS-III symbol search, Alphabet writing, simple and choice Reaction time (Go/NoGo), symbol search (WAIS-III).

Executive function domain is assessed by category test, trails test A & B, Winconsin card sorting test.

Language function is assessed by verbal fluency (phonemic and category), Boston Naming test, Thurstone word fluency, controlled Auditory word association test.

Visuoperception / visuomotor domain is assessed by WAIS-R Block design, Embedded figures test and Money's Standardised road-map test of direction sense.

Constructional abilities are assessed by WAIS-R Block design, Tactual performance test and copy a cube.

Fine motor abilities are assessed by Grooved peg board test and alphabet writing and gross motor abilities assessed by finger tapping and Grip strength.

For psychiatric assessment, following test batteries are used in various studies. They includes Diagnostic Interview Schedule (DIS), Hamilton Reading Scale for Depression (HRSD), Spielberger State-Tract Anxiety Immentary STAI, Mini mental State Examination, Beck Depression Inventory (BDI), Profile of Mood State (POMS), Structured Clinical Interview for DSM-IV and Composite International Diagnostic Interview (CIDI).

WHO Neuropsychological test batteries consists of Trail making test A, WHO/VCLA Auditory verbal learning, WHO/VCLA picture memory Interference, WAIS Digit symbol, color trails I, color Trails II, Verbal fluency (Names, animal), WAIS Block Design, Grooved Peg board, Time Gait.

Gupta et al in NIMHANS, Bangaluru, used following test batteries for assessing the neuropsychological domains and were verbal-N-Back task, WHO-AVLT, Visual N-Black Task, Tower of

London, phonemic fluency, category fluency (Animal naming), Finger tapping.

1. Digit Vigilance Test : DVT

The Digit vigilance test (Lezak, 1995) consists of numbers 1 to 9 randomly ordered and placed in rows on a page. There are 30 digits per row and 50 rows on the sheet. The digits are closely packed on the sheet. The same level of mental effort (or) attention deployment is required over a period of time. The subject has to focus on the target digits like 6 and 9 amongst other distraction digits. Inability to sustain and focus attention leads to both increased time to complete the test as well as errors. Digit Vigilance Test tests sustained attention. Frontoparietal network mediates sustained attention.

2. Digit Symbol Substitution Test (DSST):

The digit symbol substitution test (Wechsler, 1981) is a test of visuo motor coordination, motor persistence, sustained attention and response speed. Rapid information processing is required in order to substitute the symbols accurately and quickly. The test consists of a sheet in which numbers 1 to 9 are randomly arranged in 4 rows of 25 squares each. The subject substitutes each number with a symbol using a number symbol key given on the top of the page. The first ten squares are for practice. DSST is used to measure mental speed. Mental speed is a composite measure, which requires rapid processing of information and information processing speed requires coordination of different areas of the brain.

3. Triads test:

The triads test was developed at NIMHANS, Bangaluru. It combines a verbal triads task with a tactual number identification task. The two tasks differ with reference to the stimulus modality and the nature of stimulus processing. The nature of the response is similar in that both the tasks require a verbal response. Therefore it is hypothesized that the attention resource pool tapped by the two tasks are partially different. This partial overlap within the attention resource pool in terms of the overlap of the nature of response demands division of attention. Triads test assesses divided attention and is closely related to the central executive function of working memory.

4. Animal Naming test:

The animal naming test (Lezak, 1995) requires the subjects to generate names of animals for one minute. Animal naming test tests the category fluency. In category fluency, unlike in phonemic fluency, it is the content of the words, rather that the phonetic similarly of the words, that is regulated. Verbal fluency activates frontal lobes, particularly the prefrontal cortex in the language dominant hemisphere.

5. Auditory Verbal Learning Test:

The Rey's Auditory Verbal Learning Test (AVLT) (Schmidt, 1996) adopted for different cultures by WHO (Maj et al, 1994) was adopted to suit conditions in India. Rey originally developed the test in 1964. It consists of words designating familiar objects like

vehicles, tools, animals and body parts. There are two lists A and B, with different words in each list.

Prefrontal cortices are important for the organization of the material, verification of recalled material and formulating heuristic strategies for learning. Hippocampal structures are important for association between events discrete in time and space.

6. Trial Making Test (TMT) A:

Trial Making Test A consist of 25 circles distributed over a sheet of paper. A, the circles are numbered 1 – 25, and the patient should draw lines to connect the numbers in ascending order. The patient should be instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper. Time patient takes to complete is calculated. If the patient makes an error, point it out immediately and allow the patient to correct it. Errors affect the patient's score only in that the correction of errors is included in the completion time for the task.

Trial making test A assesses information processing speed, and executive function.

7. Standard Progressive Matrices:

Raven's Standard Progressive Matrices (1936) are multiple choice tests of abstract reasoning which are, also used of assessment for intelligence. It is originally developed by John C.Raven in 1936. The booklets consists of five sets (A to E) of 12 items each (eg. A_1 through to A_{12}), with items within a set becoming increasingly difficult, requiring ever greater cognitive

capacity to encode and analyse information. All items are presented in black ink on a white back ground. In each test items, a patient is asked to identify the missing segment required to complete a larger pattern. Many items are presented in the form of a 3 x 3 (or) 2 x 2 matrix, giving the test its name.

Adequate standardization, ease of use (without written (or) complex instructions), and minimal cost per person tested are the main reasons for its widespread international use in most countries of the world.

Materials & methods

MATERIALS AND METHODS

The study on neuropsychological assessment of HIV patients on ART was approved by the Institute Ethical Committee of Tirunelveli Medical College Hospital. The study was carried out from the period of March 2011 to Feb 2012.

Inclusion criteria:

i) HIV positive patients diagnosed by ELISA attending ART clinic in TVMCH.

ii) Patients age between 16 years and 65 years.

iii) Patient should be a literate (able to read and write and capable of doing neuropsychological tests).

Exclusion criteria:

ii) Patients with past (or) present neurological disorders (eg: TBM, CNS Toxoplasmosis,CVA etc)

iii) Patients with past (or) present psychiatric illness.

iv) Patients with substance abuse and dependence.

v) Patients with H/o head injury.

vi) Patients with acute severe medical illness which could interfere with the comprehension and unable to perform the study.

Methodology:

HIV positive patients attending ART centre is Tirunelveli Medical College Hospital were selected for this study. HIV positive patients who were on ART were selected for study on the basis of inclusion and exclusion criteria. The study population was explained about the purpose and nature of the study initially and informed consent was obtained from all patients.

Demographic profile of patients was collected. Age, Sex, marital status, education status, duration of HIV infection, duration of ART, ART regimen and clinical stage of HIV infection were noted.

For all selected patients, baseline CD4, and recent CD4 count were noted. All routine biochemical blood investigation like Blood Sugar, Urea, Creatinine, Liver Function Tests, complete hemogram, Chest X-ray, Ultrasound abdomen were done.
CT Brain study was done in all selected patients.

A detailed history was taken from all patients with special focus on higher cognitive functions and lobar functions. Neurologic examination was done in all patients. Detailed higher mental functions and lobar functions examination was done. Cranial nerves examination, spino motor system, extra pyramidal system, sensory system, cerebellum and autonomic nervous system were examined in detail.

Higher cognitive functions focusing on attention / working memory, sustained attention, language, learning and memory, visuo motor function, executive functions, information processing

speed, and co ordination were examined in detail. Regular higher mental functions and lobar function examination was supplemented by neuropsychological test batteries to quantity the deficits in various domains.

The clinical examination findings and neuropsychological test batteries findings were noted and results were obtained with statistical analysis.

Neuropsychological test batteries used are:

1. Digit vigilance Test (Lezak, 1995)
2. Digit symbol substitution test (Wechsler, 1981)
3. Triads test (NIMHANS, NEUROPSYCHOLOGICAL BATTERY, 2004)
4. Animal names test (Lezak, 1995)
5. Auditory verbal learning test (Schmidt, 1996)
6. Trial making test A.
7. Standard progressive matrices (Raven, 1989)

The domains studied include

1. Attention
2. Memory
3. Language
4. Cognition
5. Frontal lobe functions
6. Parietal lobe functions
7. Temporal lobe functions
8. Occipital lobe functions

Results & Observation

RESULTS AND OBSERVATION

Data and study group:

Total number of patients enrolled in this cross-sectional study is 50. Males were 26 (52%) and females were 24 (48%).

Age group:

Study population was in various age groups. Maximum age studied in this study was 59. minimum age studied was 26.

Males were aged from 27 years to 59 years.

Females were aged from 26 years to 55 years. Most common age group in our study population is from 36 - 45 years. 29 patients were in 36 – 45 age group and forms 58% of this study. Next common age group noted is 26 – 35 years. In this age group 13 patients were present and forms 26% of study population.

Age group	**Male**	**Female**	**Total**
16 – 25	-	-	-
26 – 35	4 (8%)	9 (18%)	13 (26%)
36 – 45	17 (34%)	12 (24%)	29 (58%)
46 - 55	4 (8%)	3 (6%)	7 (14%)
56 - 65	1(2%)	-	1 (2%)
Total	26 (52%)	24 (48%)	50 (100%)

Education:

In this study, patients educations status ranged from 3 years of school education to college under graduates degree education.

Most of the patients had school education. 27 patients had 6 – 10 years of school education. 21 patients had 3 – 5 years of school education. One patient had 12 years of school education and another patient had completed BA degree.

Years of education	Male	Female	Total
3 – 5 yrs of school	10	11	21
6 – 10yrs of school	14	13	27
11 – 12 yrs of school	1	-	1
College education	1	-	1
Total	26	24	50

Stage of HIV infection:

In this study, patients were present in various stages of WHO classification of HIV infection / AIDS by clinical case definition. Most common study population were noted in clinical stage III – 24 patients (48%), followed by clinical stage I.Seventeen patients were in clinical stage I (34%). 7 patients were in clinical stage II (14%) and two patients were in clinical stage IV (4%).

Of 26 male patients, 16 patients were in clinical stage III (i.e) 61.5% of male population in stage III. Of 24 female patients, 12

patients were in clinical stage I (50%), followed by 8 patients were in stage II (16%).

Stage	Male	Female	Total
I	5	12	17
II	4	3	7
III	16	8	24
IV	1	1	2
Total	26	24	50

HIV infection duration:

Patients included in study population had HIV infection duration ranging from 3 months to 10 years. Of total 50 patients, 19 patients having HIV infection 37 – 48 months, followed by 9 patients having more than 5 years of HIV infection.

HIV Duration	Male	Female	Total
< 2 years	7	3	10
25 – 48 months	13	13	26
> 48 months	6	8	14
Total	26	24	50

ART Duration:

Similarly, the study population also had varying duration of ART regimen in the treatment of HIV infection. ART duration ranged from 2 months to 6 years.

HAART Duration	Male	Female	Total
1 – 12 months	7	4	11
13 – 24 months	3	2	5
25 – 36 months	6	3	9
37 – 48 months	6	12	18
49 – 60 months	2	1	3
> 60 months	2	2	4
Total	26	24	50

ART Regimen:

The study population was treated with three drugs regimen of ART, most commonly used ART regimen in this study is ZLN (Zidovudine, Lamivudine and Nevirapine) (i.e) 25 patients (50%) were on ZLN regimen, followed by SLN (Stavudine, Lamivudine, Nevirapine) regimen with 11 patients (22%).

ART Regimen	Male	Female	Total
ZLN	15	10	25
SLN	4	7	11
SLE	3	1	4
ZLE	1	1	2
ZLN → ZLE	-	1	1
SLN → ZLN	-	1	1
SLE → ZLN	1	2	3
SLE → SLN	1	1	2
ZLE → ZLN	1	0	1
Total	26	24	50

Baseline CD4:

Baseline CD4 counts of study population were noted. It ranged from 34 to 649.

Baseline CD4	Male	Female	Total
< 200	19	16	35
201 - 400	6	7	13
401 – 600	1	-	1
601 – 800	-	1	1
> 800	-	-	-
Total	26	24	50

70% (35 patients) had baseline CD4 counts less than 200 followed by 26% (13 patients) had baseline CD4 between 201 – 400.

Recent CD4:

Similarly, recent CD4 count of study population noted. It ranged from 73 to 950. 38% (19 patients) had CD4 count between 201 – 400 followed by 34% (17 patients) had CD4 count less than 200.

Recent CD4	Male	Female	Total
< 200	15	2	17
201 - 400	8	11	19
401 – 600	2	3	5
601 – 800	-	7	7
> 800	1	1	2
Total	26	24	50

Higher cognitive function examination results:

Clinical neuropsychological examination of study population revealed deficits in various domains of cognitive functions.

Attention tested by digit forward, digit backward, Go-No-Go test, spell backward and vigilance revealed deficits in 31 patients (62%).

Attention:

ART duration	Impaired	Normal
< 2 year	12	4
> 2 year	19	15

Chi square 2.54

P value 0.11

CD4 count	Impaired	Normal
< 200	10	7
> 200	21	12

Chi square 0.0005

P value 0.9805

Immediate memory testing revealed deficits in 28 patients, (56%) of study population. Immediate memory is tested by Digit repetition (DF & DB).

Immediate memory:

ART duration	Impaired	Normal
< 2 year	7	9
> 2 year	21	13

Chi square 0.779

P value - 0.377

CD4 count	Impaired	Normal
< 200	7	10
> 200	21	12

Chi square 1.446

P value - 0.229

Recent memory evaluation done by delayed recall of words revealed deficits in 16 patients (32%) of this study group.

Recent memory:

ART duration	Impaired	Normal
< 2 year	9	7
> 2 year	7	27

Chi square 7.94

P value 0.004* Statistically significant

CD4 count	Impaired	Normal
< 200	6	11
> 200	10	23

Chi square 0.451

P value 0.501

Calculation difficulty was noted in 13 patients (26%) of study population.

Calculation:

ART duration	Impaired	Normal
< 2 year	4	12
> 2 year	9	25

Chi square 0.054

P value 0.816

CD4 count	Impaired	Normal
< 200	4	13
> 200	9	24

Chi square 0.0029

P value 0.9570

Category fluency was impaired in 6 patients (12%) of study population. Category fluency tested by animal naming test in one minute.

Fluency:

ART duration	Impaired	Normal
< 2 year	3	13
> 2 year	3	31

Chi square 2.129

P value 0.144

CD4 count	Impaired	Normal
< 200	1	16
> 200	5	28

Chi square 0.241

P value 0.623

Constructional ability was impaired in 11 patients (22%).

Constructional ability:

ART duration	Impaired	Normal
< 2 year	4	12
> 2 year	7	27

Chi square 0.504

P value 0.477

CD4 count	Impaired	Normal
< 200	4	13
> 200	7	26

Chi square 0.294

P value 0.587

Peripheral neuropathy is observed in 16 patients (32%). 8 patients each with peripheral neuropathy had taken ART less than 2 years group and more than 2 years of ART.

Peripheral neuropathy:

ART duration	Impaired	Normal
< 2 year	6	10
> 2 year	10	24

Chi square 0.79

P value 0.37

CD4 count	Impaired	Normal
< 200	5	12
> 200	11	22

Chi square 0.001

P value 0.969

Neuropsychological test results:

To supplement higher cognitive clinical examination and to quantify the neuropsychological impairments,neuropsychological test batteries were used after clinical examination.

Digit Vigilance test:

This test is used for testing sustained attention, visuo motor coordination and processing speed. 30 patients had deficits in doing DVT (60% of study group).

DVT:

ART duration	Impaired	Normal
< 2 year	9	8
> 2 year	21	12

Chi square 0.178

P value 0.672

CD4 count	Impaired	Normal
< 200	10	7
> 200	20	13

Chi square 0.032

P value 0.85638

Digit Symbol Substitution Test:

It is a test of motor persistence, response speed, visuo motor coordination and sustained attention. 33 patients had deficits in Digit Symbol Substitution Test (66%).

DSST:

ART duration	Impaired	Normal
< 2 year	14	4
> 2 year	19	13

Chi square 2.60

P value 0.10

CD4 count	Impaired	Normal
< 200	10	7
> 200	23	10

Chi square 0.201

P value 0.653

Triad test is used to assess the divided attention. 23 patients were found to have deficit while doing triads test (46%).

Triads test:

ART duration	Impaired	Normal
< 2 year	10	6
> 2 year	13	21

Chi square 3.57
P value 0.05* Statistically significant

CD4 count	Impaired	Normal
< 200	6	11
> 200	17	16

Chi square 0.61
P value 0.43

Auditory Verbal Learning Test:

Auditory Verbal Learning Test is used to assess learning and memory. 27 patients had deficit in AVLT testing (54%).

AVLT:

ART duration	Impaired	Normal
< 2 year	13	3
> 2 year	14	20

Chi square 8.564
P value 0.003* Statistically significant

CD4 count	Impaired	Normal
< 200	11	6
> 200	16	17

Chi square 1.892
P value 0.169

Trial Making Test:

Trial Making Test A is used to assess the executive function and speed of information processing. 16 patients found to have deficit in Trial Making Test A (32%).

TMT-A

ART duration	Impaired	Normal
< 2 year	8	8
> 2 year	8	26

Chi square 4.729

P value 0.029*

CD4 count	Impaired	Normal
< 200	5	12
> 200	11	22

Chi square 0.001

P value 0.969

Animal Naming Test :

ART duration	Impaired	Normal
< 2 year	4	12
> 2 year	2	32

Chi square 5.677

P value 0.017*

CD4 count	Impaired	Normal
< 200	4	13
> 200	2	31

Chi square 5.005

P value 0.025* Statistically significant

Raven's Standard Progressive Matrices:

Raven's Standard Progressive Matrices test is used for assessing the abstract reasoning. 19 patients found have impairment.

ART duration	Impaired	Normal
< 2 year	11	5
> 2 year	8	26

Chi square 11.231

P value 0.0008* Statistically significant

CD4 count	Impaired	Normal
< 200	6	11
> 200	13	20

Chi square 0.00039

P value 0.980

Analysis of study group:

In this study, detailed clinical exam of higher cognitive functions and lobar functions, cranial nerves, spino motor system, sensory system, cerebellar system, extra pyramidal system, autonomic nervous system were carried out, which was supplemented by the neuropsychological test batteries to quantify the deficits in various domains.

In this study group among the total 50 number of patients, 26 (52%) were males and 24 (48%) were females.

Patients with various age group were included in our study ranging from 26 years to 59 years. Males were aged from 27

years to 59 years and females aged from 26 years to 55 years. 58% of study population from 36 – 45 years age group (29 patients) followed by 26% from age group of 26 – 35 years (13 patients).

Mean age of this study population is 39.26 (SD 7.108).The study population were in various stages of HIV infection ranging from stage I to stage IV. Most common WHO clinical stage noted in our study is stage III (48%) followed by stage I (34%). 14% with stage II infection and 4% had stage IV disease. More number of male patients (17 patients) were in advanced stages (III & IV) than female patients (9 patients), in this study.

The duration of HIV infection ranged from 3 months to 10 years. Most of this patients had more than 2 years of HIV infection (40 patients).

In this study patients were on ART with varying duration. 16 patients (32%) had taken ART less than two years. 34 patients (68%) were on ART more than two years.

Most common ART regimen taken by study population is ZLN (Zidovudine), Lamivudine and Nevirapine) 25 patients (50%) followed by SLN (Stavudine, Lamivudine and Nevirapine) 11 patients (22%).

Baseline CD4 of this study population ranged from 34 to 649 with a mean of 175.30 (SD 116.989). 70% of study population had CD4 count less than 200 (35 patients). 26% patients had CD4 count between 201 – 400 (13 patients). 2% (1 patient) had CD4 count between 401 – 600 and 2% (1 patient) had baseline CD4 count between 601 – 800.

Recent CD4 count ranged from 73 to 950 with mean CD4 count of 331.32, (SD 222.791). 34 % (17 patients) had CD4 count less than 200. 66 % (33 patients) had CD4 count more than 200. 38% (19 patients) were with CD4 count 201 – 400. 10% (5 patients) were with CD4 count 401 – 600. 14% (7 patients) were with CD4 count 601 – 800. 4 % (2 patients) were with CD4 count more than 800.

Analysis of Neuropsychological impairment in study population:

The detailed clinical higher cognitive functions and lobar function examination done in study population revealed the deficits in various domains.

The most commonly affected higher cognitive function is attention. 31 patients were affected by attention deficits and they were able to say digit forward < 5 numbers. Digit backward performed also revealed deficits in 31 patients.

Immediate memory is affected in 28 patients of study and recent memory affected in 16 patients.

Difficulty in calculation is noted in 13 patients and unable to proceed 2 – 3 steps of serial subtraction.

Similarly 11 patients in study group had difficulty in constructional ability.

16 patients in the study population had peripheral neuropathy.

The neuropsychological test batteries used in this study subsequent to detailed clinical neuropsychological examination.

The following deficits are noted in various test batteries employed in the study.

In Digit Vigilance Test 30 patients (60%) had deficits in attention and response speed.

In Digit Symbol Substitution Test 33 patients (66%) had deficits in the motor persistence, sustained attention, visuo motor coordination.

In Triad Tests 23 patients (46%) had deficits in divided attention.

In Auditory Verbal Learning Test, 27 patients (54%) had deficits in learning and memory.

In Animal Naming Test 6 patients (12%) had deficits in category fluency.

In Trial Making Test A, 16 patients (32%) had deficits in executive functions and speed of information processing.

In Raven's Standard Progressive Matrices, 19 patients (38%) had deficits in abstract reasoning.

Neuropsychological domains	**Affected**	%
Attention	31	62
Memory	28	56
Language	11	22

Cognition	Affected	%
a)Fund of knowledge	5	10
b)Judgement	3	6
c)Calculation	11	22
d)Abstract thinking	19	38

In this study population, 31 patients had deficits in attention. Most common neuropsychological domain affected is attention (62%) followed by memory (56%).

In memory, the immediate memory was affected in 28 patients and recent memory was impaired in 16 patients. Both immediate memory and recent memory were impaired in 11 patients.

In language domain tested, all patients were able to comprehend, responded appropriately, able to read and write. Repetition were normal in all patients. 6 patients had impairment in category fluency. 11 patients had impairment in copying.

Cognition was assessed by fund of knowledge, new learning abilities, judgements, calculation and abstract thinking. 5 patients had poor fund of knowledge, 3 patients had impaired judgements, 11 patients had calculation difficulties and 19 patients found to have deficit in abstract thinking.

Frontal lobar function were affected in most of the patients in this study. Motor persistence and response speed was impaired in 33 patients as tested by Digit Symbol Substitution Test. Executive function and speed of information processing was

impaired in 16 patients. Divided attention was tested by Triads test and found to be impaired in 23 patients.

Frontal lobar functions	**Affected**	%
Motor persistence and response speed	33	66
Executive function	16	32
Divided attention	23	46

Parietal lobar functions examination of patients revealed deficit in calculation and constructional ability. Calculation impairment noted in 13 patients (26%) and constructional ability was impaired in 11 patients (22%).

Parietal lobe function	**Affected**	%
Calculation	13	26
Constructional ability	11	22

Temporal lobe examination revealed deficits in verbal memory 28 patients 56% behavioral changes were noted in 10 patients like depression.

Temporal lobe function	**Affected**	%
Verbal memory	28	56%
Behavioral changes	10	20%

Examination of occipital lobe functions in study population found to be normal in all patients.

In this study only 6 patients were found to be normal in both clinical examination of higher cognitive functions and lobar functions. The duration of HIV infection in this 6 patients ranged from 21 month to 72 months. 3 patients were in stage III, 2 patients were in stage II, and one patient had stage I infection.

Duration of HIV infection in neuropsychological affected population

Attention:

HIV Duration	Affected	Total	%
<24 months	5	10	50%
25 – 48 months	17	26	65.3%
>48 months	9	14	64.2%
Total	31	50	62%

Memory (Immediate)

HIV Duration	Affected	Total	%
<24 months	5	10	50%
25 – 48 months	16	26	61.5%
>48 months	7	14	50%
Total	28	50	56%

Calculation

HIV Duration	Affected	Total	%
<24 months	3	10	30%
25 – 48 months	6	26	23%
>48 months	4	14	28.5%
Total	13	50	26%

Constructional ability

HIV duration	Affected	Total	%
<24 months	3	10	30%
25 – 48 months	4	26	15.3%
>48 months	4	14	28.5%
Total	11	50	22%

Recent memory:

HIV Duration	Affected	Total	%
<24 months	6	10	60%
25 – 48 months	5	26	19.2%
>48 months	5	14	20.8%
Total	16	50	32%

Peripheral Neuropathy:

HIV Duration	Present	Absent	%
<24 months	3	10	30%
25 – 48 months	9	26	35%
>48 months	4	14	28.5%
Total	16	50	32%

Tests:

1. **DVT:**

HIV duration	**Impaired**	**Total**	%
<24months	7	10	70%
25 – 48 months	17	26	65.3%
>48 months	9	14	64.2%
Total	33	50	66%

2. **DSST:**

HIV Duration	**Impaired**	**Total**	%
<24 months	7	10	70%
25 – 48 months	17	26	65.3%
>48 months	9	14	64.2%
Total	33	50	66%

3. **Triads test:**

HIV Duration	**Impaired**	**Total**	%
<24months	7	10	70%
25 – 48 months	11	26	42.3%
>48 months	5	14	35.7%
Total	23	50	46%

4. AVLT

HIV Duration	Impaired	Total	%
<24 months	8	10	80%
25 – 48 months	10	26	38.4%
>48 months	9	14	64.2%
Total	27	50	54%

5. TMT-A

HIV Duration	Impaired	Total	%
<24 months	4	10	40%
25 – 48 months	7	26	26.9%
>48 months	6	14	42.8%
Total	17	50	34%

6. Animal Naming Test:

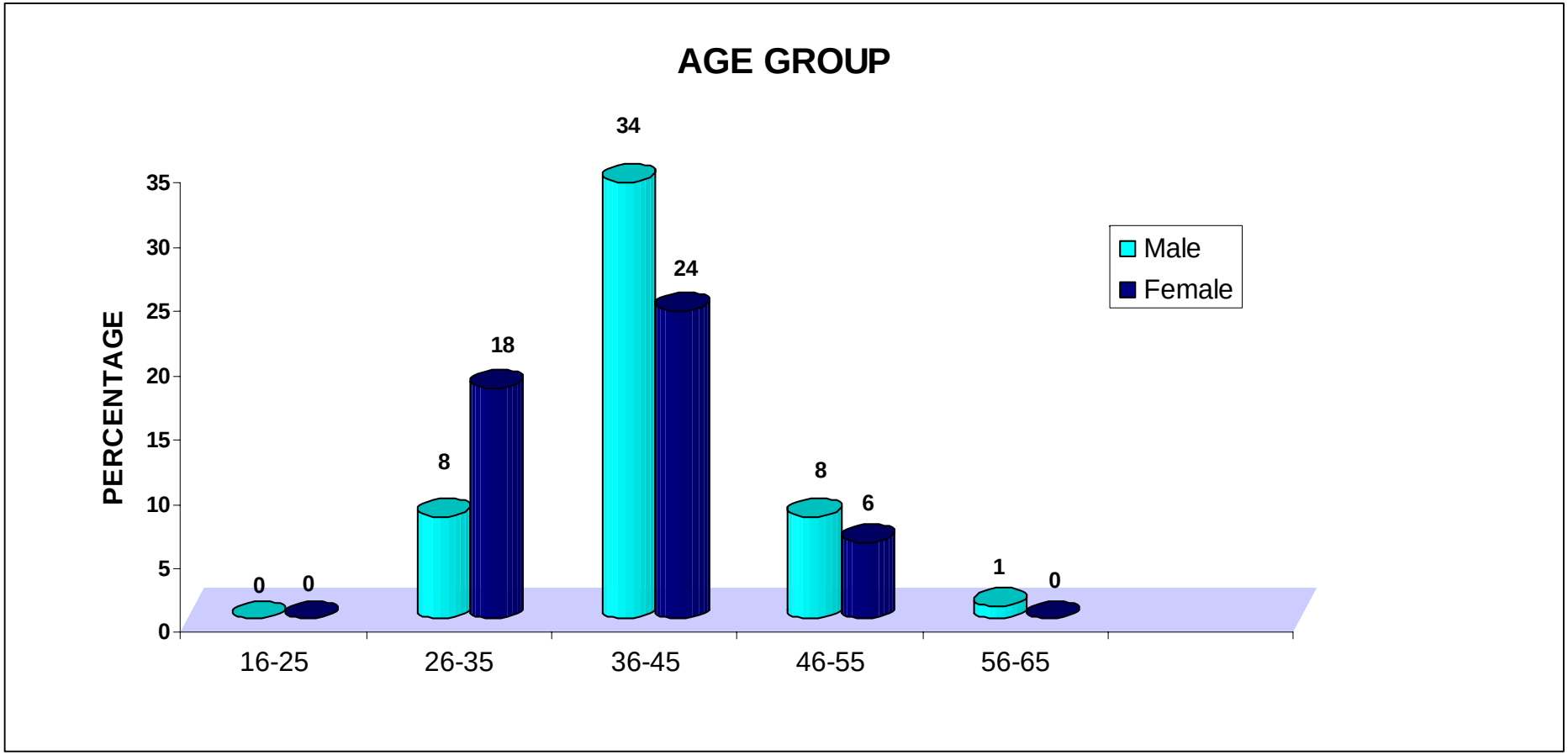
HIV Duration	Impaired	Total	%
<24 months	2	10	20%
25 – 48 months	2	26	7.6%
>48 months	2	14	14.2%
Total	6	50	12%

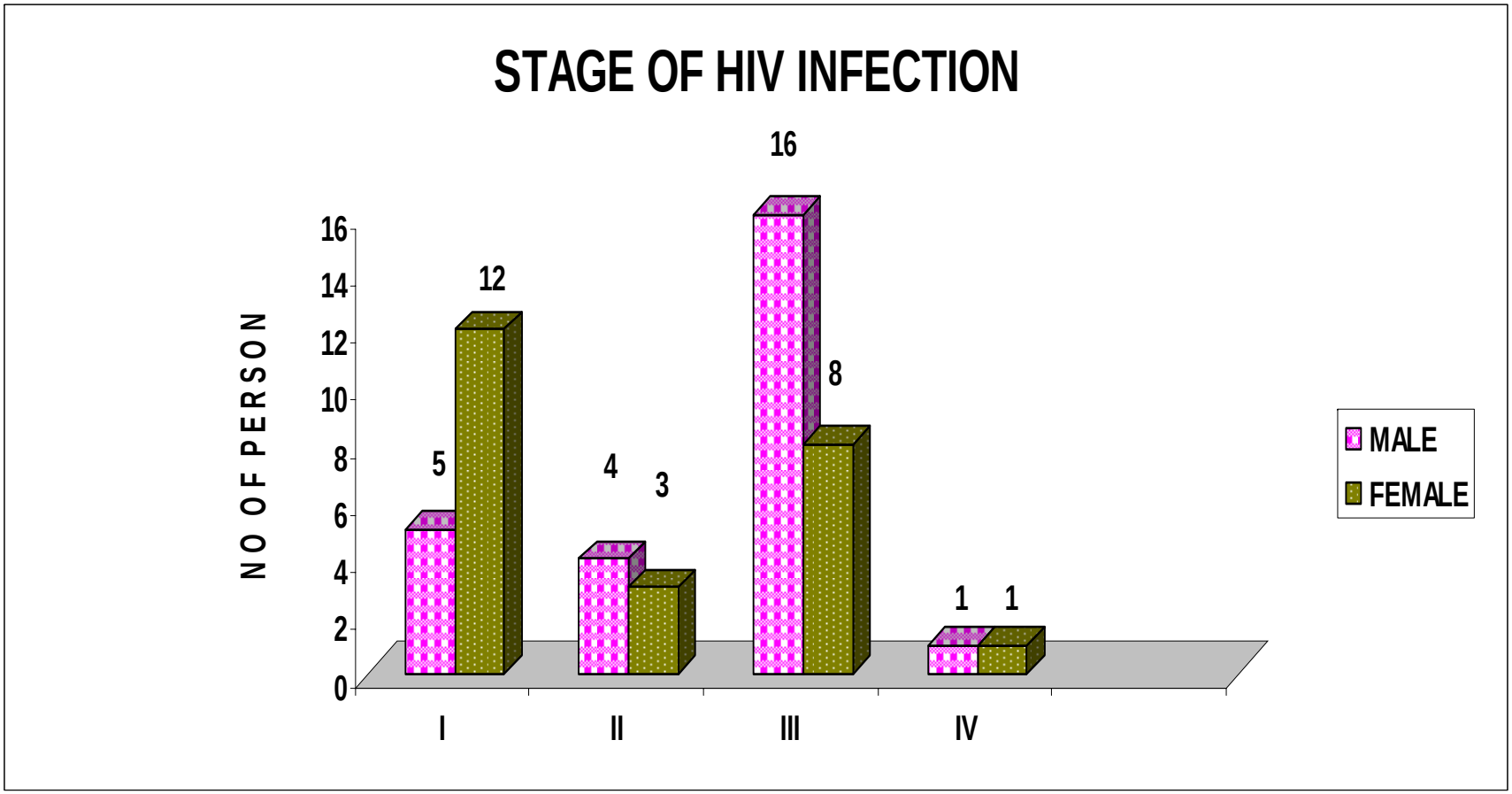
7. Raven's Standard Progressive Matrices:

HIV Duration	Impaired	Total	%
<24 months	7	10	17%
25 – 48 months	6	26	23.07%
>48 months	6	14	42.85%
Total	19	50	38%

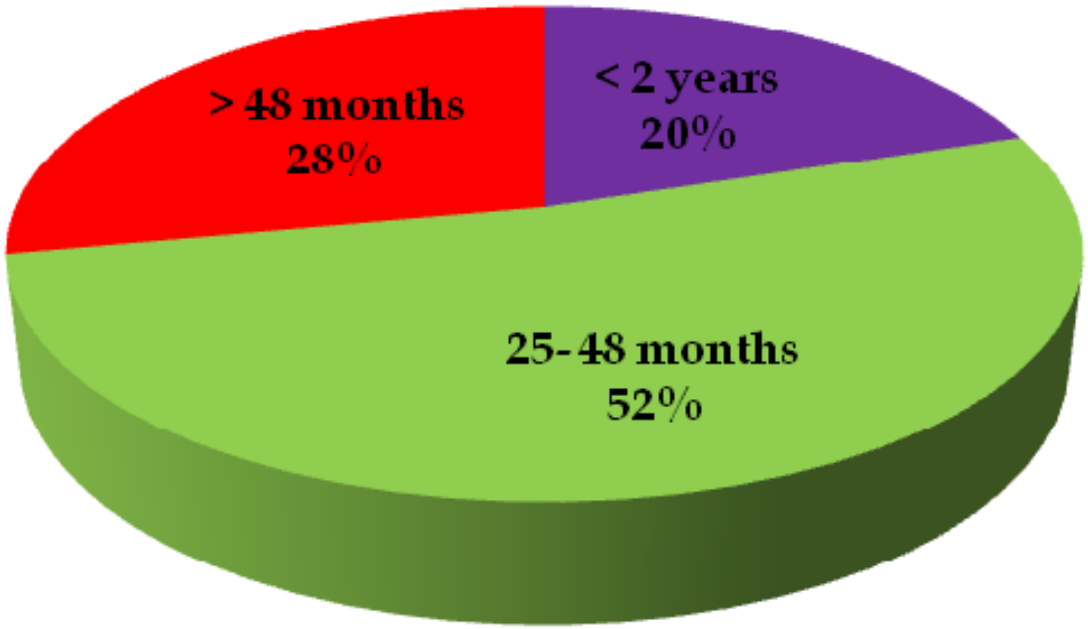
Study group	**HIV duration**			**ART Regimen**		**CD 4 count**	
	<24 months	**25-48 Months**	**>48 months**	**ZLN**	**SLN**	**<200**	**>200**
Normal	1	4	1	2	1	4	2
One domain affected	1	9	2	7	2	3	9
Two domain affected	3	5	2	3	2	4	6
>Two domain affected	5	8	9	14	6	6	16

As the duration of HIV infection increases the number of domains affected as tested by clinical neuropsychological examination increases.

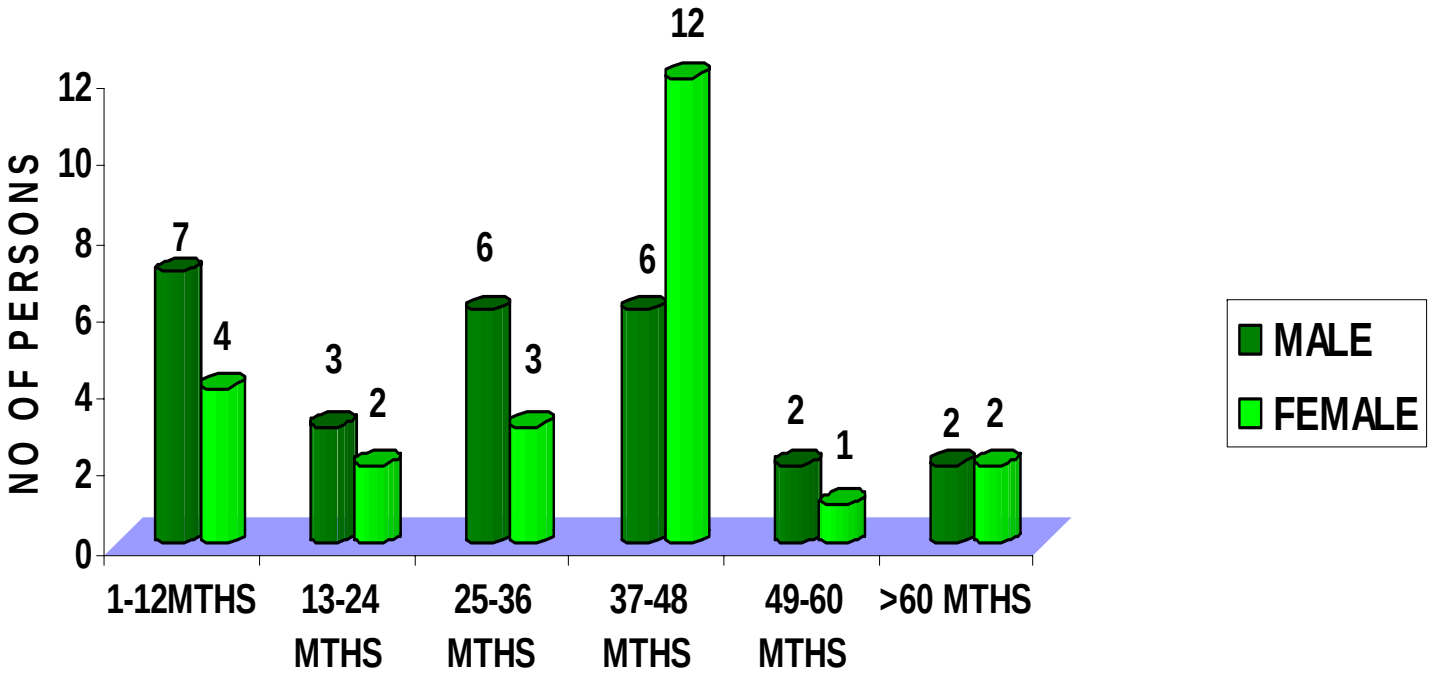

AGE GROUP
PERCENTAGE
35
30
25
20
15
10
5
0
0
0
8
18
34
24
8
6
1
0
16-25
26-35
36-45
46-55
56-65
Male
Female


STAGE OF HIV INFECTION
NO OF PERSON
0
2
4
6
8
10
12
14
16
5
12
4
3
16
8
1
1
I
II
III
IV
MALE
FEMALE

HIV DURATION



ART DURATION



Discussion

DISCUSSION

In HIV/AIDS patients, neuropsychological impairments have been well documented in all stages of infection with varying severities. Prior to the antiretroviral therapy era, HIV associated neuropsychological disorders manifested as HIV associated dementia in about 15 % of HIV positive individuals. After advent of Highly Active Anti Retroviral Therapy (HAART), the incidence and prevalence of HIV associated dementia decreased, but milder forms of neuropsychological impairments are seen in one or more domains.

Various studies quote that upto 50% of HIV -1 infected individuals will develop some form of HAND regardless of access to currently available ART.(Ellis R.et al-2007,Harezlak J et al-2011;Simioni S et -2010). Under ART, HAND has became milder,its course more protracted and variable in symptoms. It now overlaps with aging process and also with other neurodegenerative diseases in HIV/AIDS patients. The etiology of persistent neuropsychological deficits in HIV/AIDS patients on HAART remains unclear.

The first objective of this study is to determine prevalence of Neuropsychological impairment in HIV patients on ART.

In this study, the prevalence of neuropsychological impairment observed in HIV positive patients on ART is 88%.

The prevalence of neuropsychological impairments noted in various studies with varying ranges from 45 % to 86%.

Heaton RK et al in 1995 found that 86% of persons in HIV/AIDS had neuropsychological deficits.

Grant I et al in 1987 in their study found that 55% of HIV infected patients in various stages had neuropsychological deficits.

Gupta et al in 2007 in South India, Bangaluru compared 119 adults infected with HIV-1 sub type C who were not on ART with normative data derived from an Indian sample of 540 healthy volunteers with a matched cohart of 126 healthy HIV-1 sero negative individuals and found a high rate of (60.5%) mild to moderate cognitive deficits in the HIV positive patients, but no evidence of true dementia.

More recent studies conducted in HIV patients on HAART estimate that prevalence of neuropsychological dysfunction (based on neuropsychological test batteries assessments) in HIV populations. Over all 45% of cohart had neuropsychological impairment based on a global neuropsychological rating in the CHARTER study group (**Heaten et al 2009**).

Yepthomi et al in 2006 collected data in a sample of 30 treatment naïve HIV positive patients with median CD4 cell count of 97 and compared with age and education matched health controls from same region of Chennai in India showed significant differences in most of neuropsychological functions, with lower performances obtained by the HIV positive individuals and noted neuropsychological difficulties were present among individuals with sub type C virus in India with as many as 56% of the patients.

Comparison of prevalence with other studies

Study	Prevalence in %
In this study (2011 – 12)	88%
RK Heaten et al (1995)	86%
Grant I et al (1987)	55%
Gupta et al (2007)	60.5%
CHARTER Group (2009	45%
Yepthomi et al (2006)	56%

The prevalence noted in our study is high when compared with other studies except Heaten et al (1995). This may be due to detailed clinical neuropsychological examination followed by neuropsychological test batteries examination done in this study. Most of other studies were done with neuropsychological test batteries alone.

The second objective of this study is to study the pattern of neuropsychological impairment in HIV patients on ART.

The following domains of neuropsychological functions were affected with varying percentages.

1. Attention deficit noted in 62%
2. Sustained attention deficit noted in 60%
3. Divided attention deficit noted in 46%
4. Motor persistence, Response speed, visuomotor coordination deficit noted in 66%
5. Memory deficit noted in 56%
6. Verbal learning and memory impaired in 54%

7. Abstract thinking and reasoning impaired in 38%
8. Executive function impaired in 34%
9. Calculation difficulties noted in 26%
10. Constructional ability impaired in 22%
11. Animal naming test impaired in 12%

The pattern of neuropsychological impairment noted in study conducted by Stephen Ferrando et al in 1998 on HAART taking HIVpatients and not taking HAART HIV positive patients revealed following pattern of neuropsychological functions.

Verbal learning and memory is impaired in 50% of HAART taking patients and DSST test found impairment in 45% of (assessing motor persistence, response speed and sustained attention) HAART taking patients.

RK Heaten et al study on the impact of HIV associated neuropsychological impairment on every day functioning of(2004) HIV+ve patient on ART revealed that deficits among neuropsychologically impaired individuals were in domains of learning (68%), abstraction/executive functioning (54%), attention /working memory (53%), and motor functioning (47%), are noted. Least prevalent deficits were speed of information processing (36%), verbal learning (27%) and delayed recall (25%)

Another study evaluating the pattern of neuropsychological performance in a sample of HIV positive patients and HIV negative control subjects in Uganda revealed significant group differences on measures of verbal learning and memory, speed of processing, attention and executive function. This study was done by Robertson et al in Uganda in 2007.

Similarly study done by Gupta et al in India in 2007 revealed 60.5% of mild to moderate cognitive deficits and deficits noted were in attention working memory, learning and memory and fluency.

HIV enter the central nervous system early during the course of infection and cells infected by the HIV in CNS are blood derived macrophages, microglia, and astrocytes. The neurons are not directly infected with HIV. The neuronal damage occurs in HIV infection due to shed viral proteins such as gp 120 and Tat or indirectly neurotoxic molecules released by astrocytes macrophages and microglia.

Neuro imaging of HIV patients with neuropsychological impairments revealed white matter abnormalities in subcortical regions. Fronto striatal loops in the sub cortical areas commonly in HIV patients involving fronto temporal and fronto parietal circuits leading to deficits commonly observed in attention, executive functions, speed of information processing, memory, language, calculation, and constructional ability.

Third objective of this study is to find out factors that may contribute to neuropsychological impairment in HIV positive patients in ART.

Neuropsychological impairment is seen in all stages of HIV infection from stage IV to stage I.

Stage IV

Two patients were seen in stage IV HIV infection in this study. One patients show decline in one domain another patients had two domains of neuropsychological functions. Both of them

having illness more than 3 years and both showed initial CD4 count less than 200. Multiple domains involvement is not seen in either of them because , their recent CD4 count showed good improvement when compared to baseline CD4 count.

Stage III

Most of the patients in this study were in WHO clinical stage III (24 patients). In stage III 4 patients showed deficit in one domain of neuropsychological function. After analysis of these patients, we come to conclusion that even if CD4 count was less than 200 and even if duration of HIV infection varies from less than 2 years to more than 4 years, if the patient is exposed to ART very earlier, the neuropsychological impairment is less. All patients showed good response to ART as evidenced by increase in CD4 recent count and all were more than 300.

7 patients showed deficit in two domains of neuropsychological function in stage III. Analysis of this group revealed no good response to ART in term of increase in CD4 recent count. In all these patients recent CD4 count is less than 300. We hypothesise that this may be due to initial high viral load which directly affect neuropsychological functions of the brain. Duration of ART is less than one year in three patients. Five patients had not shown marked increase in CD4 count. Basal CD4 count in five patients were less than 200. Of which three patients had basal CD4 count less than 100. Thus initial very low CD4 count may also contribute to neuropsychological decline.

In patients with more than two domains involvement in stage III, analysis of results revealed that most of the patients (9 out of 10

patients) had initial CD4 count less than 200 and six of them had CD4 count less than 100. Even after the institution of ART for prolonged periods, only two patients showed improvement of more than 300 in recent CD4 count. Most of the patients were infected for more than 4 years duration. Even though many of them are on ART during this period, since their initial CD4 count were lower and even after adequate duration of ART, CD4 did not increase more than 300, we presume that initial viral load could have been more and would have caused CNS infection directly very early in the infection itself, which was smoldering.ART has exerted its beneficial role in such a way that even though multiple domains involvement is made out in this study, frank dementia is not made out in any of the patients, even though they were all clinically in stage III and many of them were infected for the previous four years.

Stage II

In stage II , two patients did not show any cognitive decline. Both patients showed initial CD4 count more than 200, and they required ART only after 24 to 48 months of initial infection. It is presumed that initial viral load was less and CNS was not affected right from the beginning. Though their CD4 count declined recently which may be due to recent increase in viral load, the neuropsychological changes may take more time to manifest outside.

In stage II, two patients showed decline in one domain. Both patients were taking ART right from the beginning and initial CD4

counts were more than 100, even though less than 200.CD4 count improvement was not more than 300.

In stage II , two patients showed decline in two domains. Both patients were exposed to ART from the beginning and initial CD4 counts were less than 200 and there was no adequate improvement in their CD4 count indicating more viral load especially in one patient in whom even after 72 months of ART, CD4 count declined from 198 to 119.

Stage I

Many of patients in stage I showed multiple domain involvement. Of total 17 patients in stage I, 10 patients had multi domain involvement. Their initial CD4 count was less than 250 in most of them(8 out of 10) and they showed good response to ART in term of increase in CD4 count(6 out of 10). But except two patients, all other patients were suffering from HIV infection for more than 3 years, some of them having HIV infection from 6 to 10 years. This long duration of HIV infection and initial low CD4 count would indicate that

1.Iinitial viral load could have been more and CNS was infected early in the illness.

2. The continuous administration of ART has prevented the development of frank dementia even after 6 to 10 years of HIV infection, but the slow smoldering effect of HIV has caused disturbances in the multiple domains of neuropsychological functions.

Analysis of study population on the basis of various stages of HIV infection from stage IV to stage I with respect to the

severity of neuropsychological impairment (no of domains of involvement of neuropsychological functions) showed interesting facts with regards to the duration of illness, initial CD4 count, recent CD4 count and early or late initiation of ART.

When analyzing patients with two domains (10 patients) involvement and more than two domain involvement (22 patients), persons having less than 200 in baseline CD4 were 23 out of 32 patients. Of these 23 patients, 10 patients initial base line CD4 count was less than 100.

Recently published study of the CHARTER group on 1525 HIV positive participants revealed that the risk of neuropsychologic impairment (NPI) was lowest in patients whose CD4 cell count was never allowed to fall to low levels before ART initiation, and suggested early initiation of ART as early as possible might reduce the risk of developing HAND, the most common source of NPI among HIV infected individuals. (Ronald J.Ellis et al – AIDS 2011). Our study also showed neuropsychological decline in multiple domains in patients with baseline CD4 count less than 100.

In this study out of 32 patients who had two domains and more than two domain involvements, 21 patients are on ART for more than 2 years of duration (9 patients had taken ART 4 years (or) more than 4 years in this 21 patients). Only 12 patients out of these 32 patients had improvement in recent CD4 count to more than 300.

So, despite ART for more than two years of duration, if there is no rise in CD4 count from the baseline, the chances of multi domain decline in cognitive function is more likely.

Late initiation of ART was observed in 4 out of 32 patients who had two (or) more domains involvement in the neuropsychological functions. Early initiation of ART might have helped to improve the CD4 count there by improvement in neuropsychological functions. A study conducted by Mc Cutchan A et al in 2007 revealed that there was no association with CD4 counts and neuropsychological impairment. But this study did not include that factor of recent increase in CD4 count after ART. However the same study Mc Cutchan A et al in 2007, demonstrated an improved performance on neuropsychological tests over a two year period from 3 to 5 years after initiating potent HIV treatment.

Long duration of HIV infection three (or) more than 3 years is also associated with neuropsychological impairment as suggested by observation that out of 38 patients with two (or) more domains involvement, 24 patients had three years (or) more than 4 years of HIV infection.

From the above following inferences are made out.

Neuropsychological changes are seen in HIV infected patients from stage I to stage IV. Absolute number of patients showing neuropsychological impairment in the multiple domains are dependent not only on clinical staging of HIV disease but also on various other parameters. From the results derived ,we understand that the initial CD4 count less than 200, and most

importantly less than 100, poor response to CD4 count improvement even after adequate duration of regular ART intake failing to increase the CD4 count to more than 300 and duration of HIV infection more than 3 years and late initiation of ART are some of the factors that contribute to disturbances in the neuropsychological functions.

Though a single variable may not indicate the presence or absence of neuropsychological disturbances and though a single variable may not indicate the severity of neuropsychological dysfunction, presence of multiple factors as discussed above may be taken to represent the presence of neuropsychological dysfunction and or its severity.When multiple factors are present, neuropsychological dysfunction in multiple domains may be expected , though converse may not be true.

Frank established dementia is not seen in study group on ART.

Conclusion

CONCLUSION

1. In this study, 88% of HIV patients on ART showed neuropsychological impairments.

2. The pattern of neuropsychological impairments noted in this study population include
   A. Attention/ working memory is affected in 62%.
   B. Executive function is affected in 32% .
   C. Divided attention is affected in 46%.
   D. Parietal lobar functions are affected in 26%. (calculation & constructional ability).
   E. Temporal lobar functions are affected in 56%.(memory).
3. Frank dementia is not observed in any of the patients studied.
4. Initial CD4 count less than 100, poor response to CD4 count improvement even after adequate duration of regular ART intake failing to increase CD4 count to more than 300 and duration of HIV infection more than 3 years and late initiation of ART are some of the factors that may contribute to disturbances in the neuropsychological functions.

Summary

SUMMARY

Neuropsychological impairments are observed in high percentage of HIV patients on ART also, causing impairments in attention/working memory, learning, executive functions, calculation and constructional ability. Initial very low CD4 count less than 100, long duration of HIV infection late initiation of ART and failure to improve CD4 count to more than 300 even after adequate duration of ART are some of the factors that may contribute to neuropsychological impairment in HIV patients on ART.

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Proforma

PROFORMA

Serial No : Date:

Patient name :

Age :

Sex : Male / Female / Transgender

Education :

Marital status :Single/Married/Separated/Divorced/widowed

Occupation :

Income :

Handedness :

Medical and lab data:

Known duration of HIV infection:

Duration of ART :

ART Regimen :

WHO stage of HIV infection : I / II / III / IV

Baseline CD4 count :

Recent CD4 count :

H/o head injury :

H/o psychiatric illness :

H/o substance abuse :

(or) dependence

H/o comorbid medical

illness : DM/HT/IHD/tuberculosis/syphilis

/Thyroid/Malignancy

H/o radiation exposure / chemotherapy

H/o exposure to heavy metals

(Mercury/Lead/Bismuth/Arsenic)

H/o drug intake Benzodiazepines/Barbiturates/Antidepressants/ Anticonvulsants/Narcotics

H/o connective tissue disorder like rash/arthralgia/fever/ Photosensitivity/alopecia

H/o exposures to commercial sex workers/Gay/ iv drug users

H/o any neurological complaints

If neurological complaints present

It onset : Acute/subacute/chronic

Course of illness : Static/progressive/fluctuating/ improves over time

H/o memory loss (eg: frequent misplacing of objects, problem with money transaction, forgets what was read (or) heard)

H/o difficulty in remembering relatives, personal and family events.

H/o difficulty in learning (or) performing new tasks.

H/o poor decision making, judgement, problem solving

H/o any change in personality : Apathetic / Disinhibited

H/o any mood change : sad/irritable/elated

H/o any behavioral changes : Aggressive/out bursts of anger if provoked/sham rage/emotional lability (or) incontinence

H/o difficulty in expression : word finding/naming/ comprehension/repeating/ reading/writing

H/o difficulty in calculation:

H/o getting lost in familiar areas (or) forgetting known routes

H/o wandering tendencies

H/o spatial disorientation within his home (or) office

H/o difficulty in dressing/neglecting one half of the body while dressing (or) shaving

H/o neglecting food on one half of the plate

H/o excessive eating (or) craving for sweets

H/o hypersexuality

H/o loss of interest in sexual activities

H/o sleep disturbance

H/o delusion / illusion

H/o hallucination : visual/auditory/olfactory/tactile/gustatory

H/o hypermetamorphosias

H/o difficulty in identifying familiar faces, objects and colours

H/o difficulty in visual perception in one half of the field

H/o cortical blindness (or) denial of blindness

H/o alien limb phenomenon

General examination of the patient:

Conscious

Oriented

Anemia

Cyanosis

Clubbing

Lymphadenopathy

Glossitis

Angular stomatitis

Icterus

Hyperpigmentation

Photosensitivity

Icthyosis

Pulse

BP

Temp

RR

Examination of Higher mental function:

I. General

- Appearance
- Handedness
- Education
- Insight
- Cooperation
- Mood/Emotions
- Denial/Neglect
- Level of consciousness

II. Attention:

- By observation
- Digit Repetition
    a) Digit forward
    b) Digit backward
- Vigilance
    a) Omission
    b) Commission

c) Perseveration

d) Go-on-go test

e) Spell backward

f) Serial subtraction

Neuropsychological tests for attention

1) Digit vigilance test
2) Triads test

III Language:

1. Spontaneous speech
    a) Fluency
    b) Sentence length
    c) Articulation
    d) Paraphasias
    e) Grammar
    f) Prosody
2. Verbal Fluency
    a) Words per minute
    b) Animal names per minute
3. Comprehension
    a) Pointing commands
    b) Yes / No commands
    c) For written languages
    d) Gestural commands
4. Repetition
5. Naming
    a) Colours

b) Objects

c) Body parts

d) Parts of objects

6. Reading
7. Writing
    a) To dictation
    b) To write body parts
    c) Write about his problems
8. Spelling
9. Copying
    a) Numbers
    b) Letters
    c) Gestures
10. Music

IV. Memory

1. Immediate memory
    a) Orientation : Date/Day/Month/Year/Time to time
    b) Orientation

    In place :Floor/Place/Town/State/Country

    c) Self
    d) Doctor
    e) Attender
    f) DF
    g) DB
    h) Verbal repetition
2. Recent memory
    a) Breakfast

b) Recall 3 words

c) Recall 3 words (improvement with clues)

d) Paired associate learning

3. Remote memory

a) Personal events

b) Family events

c) Historical events

V. Cognition:

1. Fund of knowledge

- Weeks in month
- Days of a week
- Months in a year
- President
- Father of nation
- Prime minister
- Chief minister
- Capital of Tamilnadu
- Capital of India
- National animal

2. New learning ability

a) 4 unrelated words

b) Story recall

c) Visual memory

d) Paired associate learning

3. Judgements

4. Similarities / dissimilarities

a) Scooter / Car

b) Bench / Table

5. Calculation

a) Verbal – simple / complex

b) Written - simple / complex

6. Abstract Thinking

a) Proverb interpretation

b) Conceptual series completion

Lobar function evaluation:

I. Frontal lobe function:

- Initiation defect
- Weakness
- Spasticity
- Gaze preference
- Saccades
- Anti-saccades
- Rhythmic tapping
- Fluency
- Perseveration
- Impersistence
- Alternate sequence - Fist – ring – fist test
  - Fist – palm – fist test
  - Luria's triangle
- Expressive aphasia
- Cognition/plan/goal oriented actions
- Mood

- Personality
- Behaviour
- Insight
- Apathy
- Withdrawal
- Social disinhibition
- Aggressiveness
- Outburst of anger
- Gait apraxia
- Unconcerned micturition
- Release reflexes
- Stroupe test

II. Parietal lobe function:

a) Left parietal

- Cortical sensory loss – Tactile localization/tactile discrimination
- Ideational apraxia
- Ideomotor apraxia
- Alexia
- Acalculia
- Agraphia
- Right – left orientation : Self / examiner

b) Right parietal

- Dressing apraxia
- Constructional apraxia
- Opto kinetic nystagmus

- Visual orientation – cities in map
- Hemineglect – visual / auditory / self

Both sides

Inferior homonymous quadrantanopia

III. Temporal lobe function:

Bilateral

- Superior homonymous quadrantanopia
- Hallucinations:
  Auditory/Olfactory/Visual/Gustatory
- Dreamy state with uncinate seizures
- Emotional and behavioural changes
- Delirium
- Disturbance of time perception
- Placidity
- Korsakoff amnesic defect
- Hypermetamorphosia
- Kluver Bucy syndrome

Left temporal:

- Wernickes aphasia
- Amnesia
- Verbal memory
- Dysnomia
- Amnesic aphasia

Right temporal:

- Inability to judge spatial relations
- Visual memory

- Agnosia for sounds / music
- Delirium
- Prosody

IV. Occipital lobe function:

a) Bilateral

- Contralateral homonymous hemianopia
- Unformed hallucinations – Elementary / simple
- Cortical blindness
- Loss of color perception
- Prosopagnosia
- Simultanagnosia
- Balint syndrome (optic ataxia, oculomotor apraxia, simultanagnosia)

b) Left occipital

- Color anomia
- Visual object agnosia : Apperceptive / Associative
- Alexia

c) Right occipital:

- Metamorphosia
- Topographic memory
- Visual orientation

Cranial nerves examination:

Spiromotor exam: Bulk/Tone/Power/DTR/

Involuntary movements

Sensory system evaluation : Pain, Touch, temp, vibration and joint position sense.

Romberg sign

Extra pyramidal system : Rigidity/Involuntary movement (tremor,chorea,dystonia)

Cerebellum:

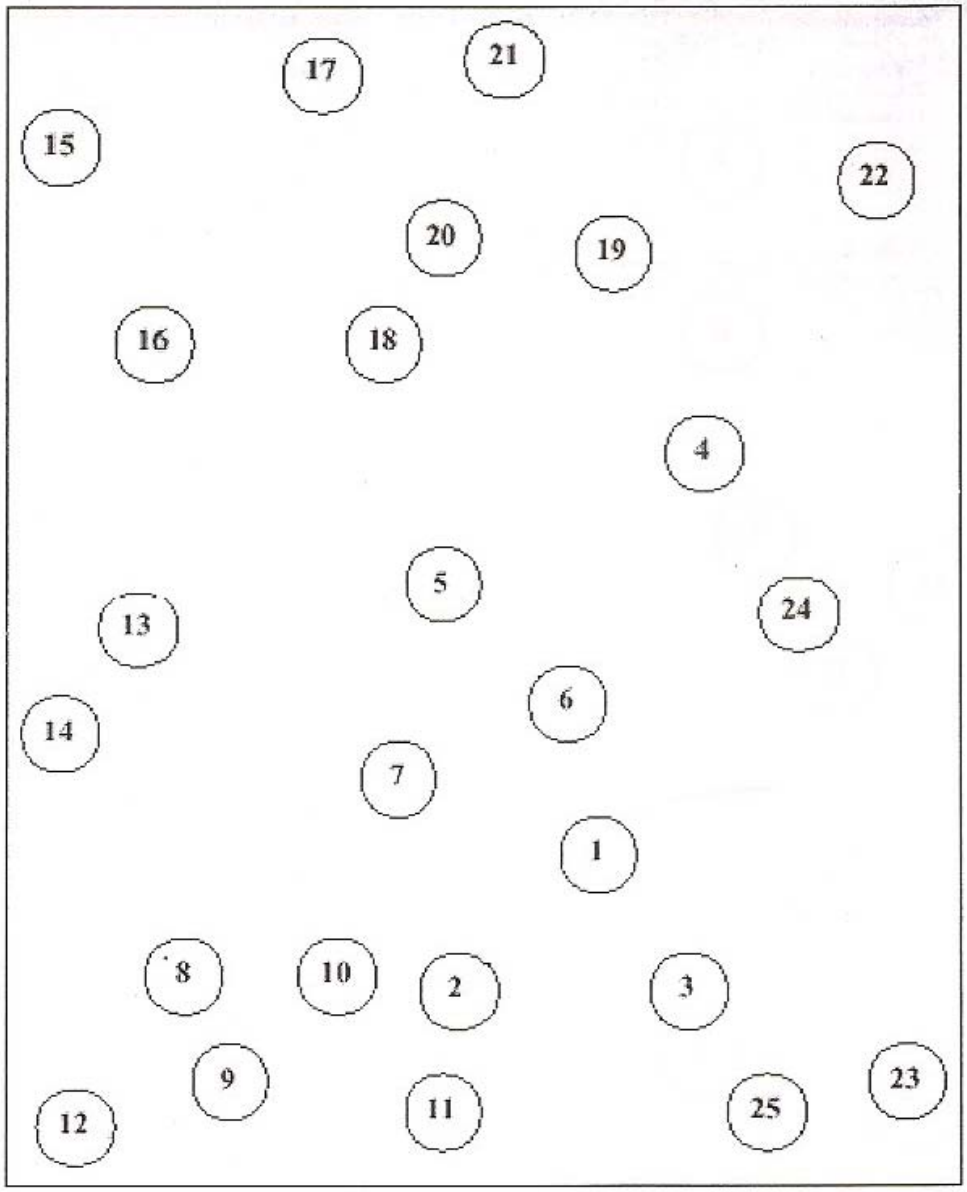
Spine and cranium:

Meningeal signs:

Gait:

Trail Making Test Part A

Patient's Name: _____ Date: _____



Appendix

AUDITORY – VERBAL LEARNING TEST

DATE:

English Version

S.No.	LIST - A	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	LIST B		IR-A	DR- A	Recognition
1	Arm						Shoes				**Hits**
2	Cat						Monkey				Mirror **Hammer**
3	Axe						Bowl				**Knife** Candle
4	Bed						Cow				Motorcycle **Axe**
5	Plane						Finger				**Clock** **Chair**
6	Ear						Dress				**Plane** Turtle
7	Dog						Spider				Leg **Dog**
8	Hammer						Cup				Table **Cat**
9	Chair						Bee				Lips Tree
10	Car						Foot				**Arm** Nose
11	Eye						Hat				Sun Truck
12	Horse						Butterfly				**Eye** Fish
13	Knife						Kettle				**Ear** **Horse**
14	Clock						Mouse				**Bike** Stool
15	Bike						Hand				Bus **Bed** **Car**

TOTAL SCORES

TRIAL 1	TRIAL 2	TRIAL 3	TRIAL 4	TRIAL 5	LIST B	IR- A	DR	RECOGNITION	
								HITS	
								OMMISSION	
								COMMISSION	

TRIADS TEST

1) Potato
   Carrot - 3
   Bus

2) Apple
   Orange - 17
   Hammer

3) Horse
   Dog - 9
   Tomato

4) Knife
   Axe - 12
   Cat

5) Eye
   Ear - 41
   Scooter

6) Brick
   Cement - 8
   Banana

7) Rose
   Jasmine - 2
   Onion

8) Pen
   Pencil - 4
   Dog

9) Hand
   Leg - 61
   Tyre

10) Camel
    Fish – 33
    Tree

11) Table
    Chair - 7
    Spider

12) Paper
    Book - 1
    Car

13) Brinjal
    Chilly - 24
    Pen

14) Lion
    Tiger - 57
    Shoe Flower

15) Aero plane
    Lorry - 5
    Nose

Neuropsychology Unit, NIMHANS- Bangalore

Neuropsychological Assessment

Name: Date:

P. No: Sex: Education: Age:

1	2	3	4	5	6	7	8	9
—	⊥	□	L	U	O	^	X	=

2	1	3	7	2	4	8	1	5	4	2	1	3	2	1	4	2	3	5	2	3	1	4	6	3

1	5	4	2	7	6	3	5	7	2	8	5	4	6	3	7	2	8	1	9	5	8	4	7	3

6	2	5	1	9	2	8	3	7	4	6	5	9	4	8	3	7	2	6	1	5	4	6	3	7

9	2	8	1	7	9	4	6	8	5	9	7	1	8	5	2	9	4	8	6	3	7	9	8	6

ID Number:
Neuro Number:

Serial No. Name Age Sex Date 12x0 C

Total Time Errors O C

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S.No	Age	Sex	Education	Occupatior	Marital sta	HIV duratic	ART durati	base line C	Latest CD4
1	39	1	5	1	4	15	14	39	129
2	37	1	7	7	4	120	26	179	247
4	40	1	7	2	1	39	39	108	237
6	36	1	8	2	1	66	60	216	718
9	37	1	8	1	4	15	1	350	298
12	34	1	4	2	1	72	2	377	622
13	32	1	5	2	1	48	1	284	104
14	34	1	8	2	4	60	12	649	613
20	38	1	5	2	1	18	18	215	237
22	39	1	3	2	1	75	75	128	414
24	50	1	4	1	4	36	36	148	833
31	27	1	5	2	1	51	48	286	722
33	36	1	8	1	4	48	48	112	280
34	43	1	5	1	4	39	39	124	328
36	40	1	7	2	1	48	48	37	263
39	45	1	5	1	4	36	36	160	242
40	49	1	5	1	4	46	46	180	395
44	32	1	10	1	1	51	48	360	654
45	26	1	8	2	1	48	48	94	420
46	35	1	9	1	1	42	42	142	576
47	37	1	8	1	1	48	48	160	734
48	35	1	9	2	1	48	48	140	219
49	55	1	5	2	1	39	38	180	339
50	30	1	10	2	1	72	70	163	791
3	59	2	3	6	4	48	24	255	253
5	49	2	12	1	1	21	20	58	194
7	40	2	3	1	1	72	36	184	104
8	29	2	5	3	2	8	6	189	189
10	36	2	4	1	1	72	72	56	321
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23	27	2	10	3	1	12	12	209	261
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26	27	2	15	1	2	27	3	196	134
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30	41	2	7	1	1	36	36	56	166
32	41	2	8	1	1	48	48	150	160
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37	36	2	9	1	1	48	48	116	192

38	45	2	10	1	1	48	48	34	218
41	40	2	8	1	1	42	36	442	232
42	39	2	8	1	1	52	52	95	142
43	49	2	10	1	1	48	48	39	200

STAGE	ART REG	attention-D	DB	Vigilance	Go-No-Go	Spell backv	Serial subtr	Lan-spon s	FLUENCY
III	2	2	2	2	2	2	2	1	1
I	2	2	2	2	2	2	2	1	1
III	3	2	2	2	2	2	2	1	1
II	1	2	2	2	2	2	2	1	1
III	5	1	1	1	1	1	1	1	1
I	1	1	1	1	1	1	1	1	1
II	2	1	1	1	1	1	1	1	1
III	2	1	1	1	1	1	1	1	1
I	1	2	2	2	2	2	2	1	1
I	1	2	2	2	2	2	2	1	1
I	1	2	2	2	2	2	2	1	1
I	2	1	1	1	1	1	1	1	1
IV	1	1	1	1	1	1	1	1	1
I	1	1	1	1	1	1	1	1	1
III	6	2	2	2	2	2	2	1	1
III	4	2	2	2	2	2	2	1	1
III	8	2	2	2	2	2	2	1	1
I	7	1	1	1	1	1	1	1	1
I	7	1	1	1	1	1	1	1	1
III	2	2	2	2	2	2	2	1	1
I	2	2	2	2	2	2	2	1	1
II	1	1	1	1	1	1	1	1	1
I	1	1	1	1	1	1	1	1	1
I	1	2	2	2	2	2	2	1	1
I	1	2	2	2	2	2	2	1	1
III	3	1	1	1	1	1	1	1	1
III	3	2	2	2	2	2	2	1	1
II	1	1	1	1	1	1	1	1	1
III	1	2	2	2	2	2	1	1	1
I	1	2	2	2	2	2	2	1	1
III	1	2	2	2	2	2	2	1	1
II	1	2	2	2	2	2	2	1	1
II	1	1	1	1	1	1	1	1	1
II	1	2	2	2	2	2	2	1	1
III	2	1	1	1	1	1	1	1	1
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I	1	2	2	2	2	2	2	1	1
I	1	2	2	2	2	2	2	1	1
III	1	2	2	2	2	2	2	1	1
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IV	3	2	2	2	2	2	2	1	1
III	2	2	2	2	2	2	2	1	1
III	2	2	2	2	2	2	2	1	1
I	1	2	2	2	2	2	2	1	1
III	7	1	1	1	1	1	1	1	1

III	2	2	2	2	2	2	2	1	1
III	1	1	1	1	1	1	1	1	1
III	1	2	2	2	2	2	2	1	1
III	8	1	1	1	1	1	1	1	1

COMPREHE	REPETITIO	NAMING	READING	WRITING	SPELLING	COPYING	MEMORY-I	RECENT M	REMOTE M
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PERSEVERA	IMPERSISTI	ALTER SEQ	BROCA API	PERSONALI	BEHA CHAI	GAIT APRA	UNCONCEI	RELEASE RI	PA-TA LO
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GRAPHEST	STEREOGN	IDE APRA	IDEOMO A	DRES APR	CONS APR	OKN	HEMINEGL	ALEXIA	ACALCULIA
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AGRAPHIA	R/L ORIE	INF QUADF	WER APHA	VERBAL MI	AMNESIA	DYSNOMIA	VISUAL ME	VISUOSPAT	HALLUC-AU
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HALL-VIS	HALL-GUS	HALL-OLF	SUP QUAD	KORSO AM	KLUVER BU	COLOR AGI	VISU-APPEI	VI-ASS-AG	VISU-ORI
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TOPO ME	METAMOR	CONT H HE	UNF VI HA	CORTICAL	PROSOPO	BALINT SY	SIMULT	C R NERV	MOTOR
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SENSOR	P N	EPS	CEREBELLU	SPI&CRA	B & BOWEI	ANIMAL N/	Triad test	AVLT 1	AVLT2
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2	2	1	1	1	1	14	12	4	6
1	1	1	1	1	1	13	9	6	9
1	1	1	1	1	1	9	10	5	7
2	2	1	1	1	1	10	11	7	9
2	2	1	1	1	1	14	12	6	8
1	1	1	1	1	1	11	12	6	8
2	2	1	1	1	1	7	11	4	3
1	1	1	1	1	1	12	10	6	8
1	1	1	1	1	1	14	8	7	9
1	1	1	1	1	1	12	11	5	7
2	2	1	1	1	1	12	9	7	8
1	1	1	1	1	1	10	11	6	7
1	1	1	1	1	1	14	8	8	5
1	1	1	1	1	1	9	12	3	3
2	2	1	1	1	1	16	5	8	9
1	1	1	1	1	1	12	10	7	8
2	2	1	1	1	1	14	8	7	10
1	1	1	1	1	1	14	10	7	9
1	1	1	1	1	1	12	10	6	8
1	1	1	1	1	1	14	11	7	9
1	1	1	1	1	1	15	7	7	9
2	2	1	1	1	1	14	8	7	8

1	1	1	1	1	1	12	6	6	8
2	2	1	1	1	1	13	10	6	8
2	2	1	1	1	1	12	9	7	8
1	1	1	1	1	1	12	6	6	8

3	4	5	Total NC	LIST B	IR NC	DR NC	RAVEN MA	MMSE	Trial makin
6	11	9	34	3	5	6	18	22	75
7	9	8	38	2	6	6	17	23	90
10	12	11	51	5	7	8	13	22	120
8	10	11	42	4	4	5	28	25	135
10	9	10	39	3	5	4	15	24	95
5	8	7	31	2	4	5	14	21	120
8	10	9	39	4	3	5	20	25	90
7	6	7	31	2	4	4	13	28	65
8	10	10	40	3	3	3	22	30	70
8	9	11	41	2	3	3	25	26	210
8	9	7	34	3	4	4	18	15	105
8	8	9	37	3	4	4	18	23	80
9	11	10	44	4	6	6	22	27	70
8	8	9	37	2	4	6	20	23	85
8	10	9	41	3	5	7	22	26	70
8	9	9	38	3	4	6	18	24	75
8	10	9	41	3	6	5	20	25	70
10	11	12	51	5	9	8	28	29	40
9	11	10	45	3	6	7	24	27	65
10	10	11	45	4	9	8	22	26	60
11	12	12	51	6	7	7	26	29	50
9	9	10	41	3	8	7	22	26	70
7	8	8	35	3	3	4	18	23	85
10	11	12	49	5	6	7	26	29	50
7	9	8	34	2	4	4	17	20	85
12	11	13	51	6	8	8	36	28	48
8	10	9	39	3	5	5	11	21	120
10	11	9	46	4	5	6	16	22	105
9	9	10	42	3	4	5	18	25	90
9	9	11	43	3	5	5	19	26	80
7	6	7	27	2	3	4	18	18	90
7	9	10	40	4	4	5	23	24	75
8	10	11	45	5	5	6	29	28	55
7	8	7	34	2	3	4	26	30	85
10	9	11	45	4	5	5	27	30	50
9	6	6	34	4	3	4	17	22	75
7	9	9	38	4	4	6	10	29	30
3	3	4	16	2	2	2	5	25	205
10	9	10	53	5	7	9	30	30	60
10	9	10	44	4	4	6	24	27	70
9	11	12	49	4	7	8	23	29	65
10	9	11	46	5	6	6	21	27	65
9	8	10	41	3	5	6	20	25	70
11	10	10	47	3	5	7	23	26	60
9	11	11	47	4	6	8	26	28	50
10	11	10	46	5	6	8	21	25	55

9	11	11	45	4	5	7	20	25	60
9	11	11	45	4	5	7	22	26	60
7	9	9	40	3	6	6	21	25	70
8	10	9	41	4	4	5	23	26	55

DVT-TT--EI	DVT-ERROI	DSST-TT-EF	DSST-ER
1560	0	1080	2
780	2	420	2
1020	45	1680	15
480	18	360	3
960	3	480	0
900	6	840	12
1200	11	1440	21
720	2	600	1
1020	7	750	2
2400	2	1800	28
1800	4	1200	11
1260	4	720	4
960	5	520	0
1050	12	780	3
1020	6	540	0
1080	4	720	2
1020	6	750	1
1020	2	600	0
960	6	720	0
900	8	780	0
1020	4	660	0
930	7	520	0
1080	12	900	2
900	2	480	0
900	45	1200	20
300	7	180	0
960	8	840	7
420	7	300	2
1020	17	840	4
1020	14	720	2
2580	20	1500	7
1020	8	780	5
660	0	420	0
960	12	650	4
840	4	600	0
1860	12	1020	3
1320	0	720	0
2260	5	1320	6
930	6	290	0
1020	6	330	2
780	8	300	0
960	10	480	0
1020	8	650	2
900	3	480	0
900	2	300	0
940	5	480	0

1020	2	600	0
960	10	630	0
1020	8	660	0
1140	4	620	0